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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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LEVERAGING REGISTRIES WITH MEDICAL DEVICE DATA FOR POSTMARKET SURVEILLANCE AND EVIDENCE APPRAISAL THROUGHOUT THE TOTAL PRODUCT LIFE CYCLE

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SESSION I: UNDERSTANDING DEVICE REGISTRIES IN THE CONTEXT OF HEALTH CARE SYSTEMS

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SESSION IV: WHAT CAN WE LEARN FROM INTERNATIONAL EFFORTS?

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M E E T I N G

(8:15 a.m.)

DR. MARINAC-DABIC: Good morning and welcome to the third day of the FDA public meeting series focusing on postmarket surveillance. I would like to thank you all for staying with us this third day and also to thank our audience that is joining us via web. We also have a great pleasure to have a wonderful international representation with representatives coming from Brazil, from Singapore, also from Canada, from Japan, Australia.

All of those colleagues would like to learn from us and also to share with us their experiences in terms of the needs for registries, the development of the registries that they have in their countries, so I think it's going to be a really wonderful exchange of information that we've always welcomed here as we try to put this national system together for the better surveillance of medical devices.

I know that some of you did not have a chance to be here for the first day and for the second day, so I'm going to maybe spend a couple of minutes just to recap some of the themes that we've heard and some of the direction where CDRH is going with regard to the surveillance of medical devices.

During the first day Dr. Jeff Shuren laid out the national postmarket surveillance plan and strategy that focuses on four pillars. You probably had the chance to read the recently released white paper, and if you

didn't, again we would encourage you to do so. We believe there is a lot of important information, not only about the Center vision, but also some really detailed examples of how those things would work in the real world as we start implementing the strategy.

So you've seen that we will focus the new surveillance system development on four elements. The first one is the development of the UDI system. And a lot of work has been done already, but a lot of work is ahead of us. That's a very important element of this transformation because the option of the UDI is going to give us an opportunity to do device-specific research. And currently we have not been able to do that. We have not been able to tap into a lot of rich data that exists just because there is no specific device identification.

Then the second element of our national postmarket surveillance strategy focuses on registries. The development of the registries, the leverage of the registries that currently exist, and creating a system that's integrated where we can all learn from each other's experiences and utilize the registry data for many different purposes.

The third pillar of the strategy focuses on modernizing the adverse event reporting and analysis. And we've heard during the first day specific steps that CDRH would like to take to make this happen.

And, finally, the fourth element of the strategy focuses on advancing the methodologies for evidence generation, appraisal, and

evaluation throughout the total product life cycle. We've heard during the first day a lot of great ideas: where are the gaps, where we need to focus because without the proper methods and the proper infrastructure for collecting and analyzing the data, we are not going to be having the best information that we can share with the public, with the patients, with clinicians, and all interested stakeholders.

Based on those four elements, we are going to be working with all of you, first of all during these four days, to hear your immediate feedback. Is something missing? Does something need to be added to the strategy? Are there areas that we should focus more or focus less? Are there areas that you would like to work with us on to make sure they are implemented? All of these are important. It's the beginning of a very important dialogue.

Then, yesterday we held, as you know, the MDEpiNet meeting, which highlighted the role of the Medical Device Epidemiology Network as the core -- as the driving force behind this postmarket transformation and postmarket surveillance development of the national system. We heard from our methodology center in Harvard and updates on ongoing methodological projects. We heard from our infrastructure and science center in Cornell/Kaiser about the projects that are ongoing with regard to building the infrastructure.

Then we tackled also an issue of what methods are needed for

making the Device Sentinel system. As you know, the FDASIA gave us the authority to set up the Sentinel system for medical devices. And, we will be working certainly on leveraging the experiences and the lessons learned from our colleagues from CDER and other centers within the FDA, but this is going to be our system. Medical Device Sentinel system is going to be built on the principles that are important to us that are evaluating medical devices. We cannot completely extrapolate what was learned and just call it Device Sentinel. We have needs that are unique, and that's why we are here today to actually talk about these needs.

Then, finally, we had a very interesting panel at the end of the day yesterday when we had almost 11 -- actually, there were 11 panelists that ranged from professional societies, academia, publishers, FDA, and other sister agencies, and talked about how we can put this together. A number of themes have emerged during yesterday's meeting.

One theme is even though this is called postmarket surveillance strategy, it actually has all fingerprints and all attributes of total product life cycle. So we would like to work together to make sure that this is also better understood by all stakeholders. This is the transformation or the strengthening of the postmarket surveillance, but we would like ultimately to have the implications for the entire TPLC. We would like to bring the information back to our premarket colleagues, back to industry, back to other stakeholders so then when we design new generation of medical devices or

we are trying to leverage or make more efficient studies in the future, we can actually rely on the data that are collected in the real-world setting.

We also heard a theme on public-private partnership. That's a very important one. From the get-go of the establishment of the MDEpiNet, we said we are going to make it public-private partnership. This was not meant to be only FDA enterprise. We wanted for all of you and for all of us to call it our public-private partnership. We are not going to be running the MDEpiNet only from the FDA. We would like -- we are under the timelines to make sure that this is finalized in terms of all the procedures and starting to actually finalize the paperwork and formalization of the public-private partnership by the end of this calendar year. So we are under the tight timeline to make sure this is really truly a public-private partnership.

And then the third theme was a need for global aspect. Although we are here to certainly develop the system for the United States, we all agreed that not taking advantage of the global data that are available in many countries and in many data sources in the areas where devices sometimes appear on the market before they are approved or cleared here in the United States, this is again another area that distinguishes us from some approaches that have been taken under the FDA Sentinel where we really in the medical device world believe that more than in other medical product areas, we need to rely on the cohesive, strategic, integrated, coordinated approach with other countries and different platforms: the platform of

regulatory agencies, also methodological, clinical and others.

These are some of the themes for those of you who actually missed the first two days that we would like now to carry over to the next two days. Because we already running a little bit late and there is a number of speakers that we would like to make sure have a chance to give their presentations, I am going to have only one slide that I'm going to try to kick off the discussion with.

Some of you may have already saw it, but I think it's useful to go through a brief exercise on -- and I'll try to make sure you actually see it -- to go through a brief exercise on how we at CDRH see the registry and other data sources evolving throughout the next couple of decades and how the larger strategy at CDRH is built on this vision that we are not going to be imposing additional burden on the data holders or the ones that are housing the registries or the clinical community, but how we are working better to integrate the data that resides in existing data sources as we try to design the postmarket surveillance strategy.

Let's start slicing this slide into little pieces. Let's start from what we currently have. During the last couple of years and up to maybe the next couple of years, we've seen certainly important developments in the policy level and the legislation that we were given and in a number of developments that set the stage, and maybe we could spend some time on actually examining those.

We have HITECH, we have ARRA, and then HITECH Act, and we also have 125 million lives in Mini-Sentinel. We heard yesterday an update that they're almost reached their -- actually they did reach their target for the last year. And so, this is their only -- these are very important data sources for all of us that are involved in the safety and effectiveness assessment at the FDA.

We also see in the MDEpiNet launch in 2010 and -- as we said the FDA had already committed over $10 million to the development of the MDEpiNet. Some of this money is already awarded. Some of the funds are going to be awarded within this week as we are moving toward the end of this fiscal year. But this is a huge commitment on our part to lead this effort and to help this effort thrive.

Then we also saw this year in the legislation, new legislation there is a call for an authority to set up the Device Sentinel. That's a very important external driving force that is -- that I think we all should take advantage of as we try to work closely to improve the surveillance. And then we also had the proposed rule, UDI rule. And we are under the tight timelines to actually have the final rule issued by May of next year.

What is going to happen, as we estimate, in the next five years? We hope that the evaluation of the UDI within claims and electronic health record will continue. And, we certainly know that a lot of you already are thinking about this and actually doing this as we speak. We also hope that

the linkage of registries and other healthcare data sources will occur because a lot of data that is currently collected in the registries is collected in other data sources. And, we would anticipate the use of the distributed data network will happen for the device surveillance.

We heard yesterday the strategy about FDA's vision also not to create new additional data sources or new mandates, but rather to be able to leverage what is already being collected and try to utilize the data that it's collected for for our own purposes.

Then in the next five years we believe the device registries and UDI registries will be fully integrated into patient healthcare dataset and that patient information will be able to be tracked via hashing or phaseologic thinking in terms of how you can actually get the longitudinal data across different data sources.

Then in the five years that follow, we would hope that postmarket infrastructure would allow for most evaluation be done via automated data collection. And, when that's not possible, we still think that there is going to be need for studies or surveys or disease-based registries.

And, finally, we believe that even though if we achieve all these things in the next couple of decades, we will still need to work on innovative methodologies and utilize them to better understand safety and effectiveness of medical devices. And, the ongoing evaluation used will provide context for benefit/risk balance for newly developed devices.

And, what I mean by this is, we talked yesterday about the need for comparisons group. We talked about the context of why this information is necessary because patients will always ask what this means for me and how this can be -- with regards to what you are actually evaluating this particular new technology. So I think that infrastructure that we are developing is going to have a huge importance on making sure that newly approved devices are looked upon within the context of what is available for the patients.

Let us now go down this slide and examine what are the data sources that we currently have in place and how we predict their utilization will actually happen during the same timeframe that I just talked about.

Maybe we can start first with the medical device reports and MDR. And, we've heard about the limitations yesterday and the day before. We talked about what we are trying to do to modernize it. We also talked briefly about mobile apps that we are developing and help developing actually in corroboration with our colleagues in academic sites to make this more accessible for patients. And, we predict that you're going to receive somewhat increased number of reports, which is again represented on the top of the slide. But, again, that's not the only source that we are going to be basing the information in the postmarket surveillance.

We also have the enhanced surveillance. And, Tom Gross presented yesterday about some of the examples, including our MedSun at

local hospitals and a number of other strategies that focus in this what we called enhanced surveillance bucket of our tools.

Then we also have de novo data collection. And, I know that industry might be interested in hearing this, that we do predict that de novo data collection for postmarket surveillance might be decreasing. As we grow stronger national infrastructure, there might be the questions that cannot be -- that do not need to be addressed by each company designing their own study that is going to be conducted during the five years post-launch and address specific questions.

We might be able actually to utilize the registries and other data sources as platforms where we can amass the post-approval studies or maybe even address them through the registries through the data collection that we all agree upon at the time when that registry is set up.

We also have the Sentinel Initiative. That's very important, and even though the Sentinel Initiative had focused primarily on drugs during the last several years, we have been working very closely with colleagues from CDER and also conducted a number of our pilot studies that focus on medical device technology that utilized the claims data and other data sources as a part of the Sentinel Initiative.

We certainly know that currently the Sentinel is focusing primarily on claims data, but there are going to be other data sources that are going to be utilized. And, we know the limitation of those data sources for all

the questions that we might have in the medical devices, but we would also like to leverage the existing infrastructure to make sure that that is available to us.

As you can see, we do predict that the use of administrative claims data will increase especially with the UDI implementation because those data sources then will have important information about device specific for our research. And, certainly the electronic health records, their use is going to increase. We hope to hear today also a lot of great presentations about your angle and your perspective on EHRs and what are their potential for device surveillance.

Then we also like to think about device registries and the registries that contain device data. Here we've just listed one recent example that FDA helped to develop. I know that Art Sedrakyan and Liz Paxton are going to talk today more in detail, but again, this is just an example of the types of the leadership that FDA had provided in motivating a lot of international registries to work together.

And, now we do have this international consortium that has representation from 15 countries with 30 registries being part of the international consortium. And, all together we do have information in those registries that is approximately 3.5 million procedures, which is really a huge step forward in the way how much we can do in the area of orthopedic devices in comparison to what we were able to do in the preceding years.

The utility of registries will increase with accurate and timely data collection. And, collecting data from EHRs or directly from patients will enhance the long-term capabilities while removing burden from healthcare facilities. And, I know that a number of you are actually working on the methodologies how to do that, how do reach patients, how they can contribute more in this exercise.

Most data currently captured in registries is also captured by the facilities at the time of the procedure. Again, we need to think about what is an extra burden on having the healthcare providers also entering the data in the registries. And, preparation and utilization of this data from the EHRs and claims data allows for better understanding of medical device use in the context of other healthcare utilization and provides additional data regarding patient outcomes.

Again, this goes in the context of what is the landscape? What else is available? So we need to not only collect the device information but other therapies in order to make sure that the proper determination of benefit/risk balance is actually appropriate and up to date.

And, finally, with all these evolving data sources and potential that they present for us, we are still going to continue doing secondary analysis of previously collected data through meta analysis, cross design synthesis, and many other methods that we heard yesterday from Sharon-Lise that she is working on to help us move the methodological field

forward in the context of medical devices.

How does MDEpiNet fit into this? As we mentioned on the first day and on the second day, MDEpiNet plays and will play the core role in all these four elements of the postmarket strategy. We believe the postmarket infrastructure and normal methodologies are going to be systematically developed and enhanced via MDEpiNet. And, this is just the beginning of a very exciting journey. I am very enthusiastic that all of you will continue to work with us.

Just the fact that so many of very important and high level and brilliant people were ready to drop everything that they were doing and on a short notice come, and some of you actually learned about this meeting last week, and still we were able to get almost everybody that we invited to come. So this tells me that that is our infrastructure. And, if we have right people at the table, I think we can get this done. And, if we also stick to the practical aspects of it, making sure that we don't forget that there is some low hanging fruit that we can accomplish as we build step by step the better surveillance for America and globally. So thank you very much.

I would like now to introduce Greg Daniel who is going to be our moderator for the first session. And, also all the panelists and speakers that they're presenting in the first session, I would like to ask you to take a seat in the front table so we can move on with the rest of the agenda. Thank you.

(Applause.)

DR. DANIEL: Okay. Thank you, Danica, and good morning everybody. My name is Greg Daniel. I'm Managing Director at the Engelberg Center for Health Care Reform at Brookings. I'm very happy and delighted to be moderating this morning's session, which is titled Understanding Device Registries within the Context of Health Care Systems.

A number of very unique perspectives will be presented today, and it'll be interesting to hear all of these perspectives and how these device registries that are currently in implementation and being conducted will fit into the very abstract art piece that Danica just went through.

With that, I think what we can do is just go around very quickly and have brief introductions from everybody, and then we'll kick off the discussion with Rick Kuntz.

DR. MACK: I'm Mike Mack. I'm a cardiac surgeon at the Baylor Health Care System in Dallas. I'm the immediate past president of the Society of Thoracic Surgeons and the chair of the steering committee of the TVT valve registry of the STS and ACC.

DR. MILLER: Good morning. I'm Dr. Marissa Miller. I'm with the National Heart, Lung and Blood Institute. I run the Advanced Technologies and Surgery Branch, and I'm intimately involved in the INTERMACS registry.

DR. BERLINER: I'm Elise Berliner. I'm the Director of the

Technology Assessment Program at the Agency for Healthcare Research Quality.

DR. DREYER: Hi, my name is Nancy Dreyer. Good morning everybody. I'm the Chief of Scientific Affairs for Quintiles Outcome, and I'm a senior editor of the registries handbook for AHRQ.

DR. GRAVES: Good morning. I'm Stephen Graves. I'm the Director of the Australian orthopedic association, National Joint Replacement Registry. I was the inaugural president of ISAP, the International Society of Arthroplasty Registries, which was formed in 2004. And, currently I'm chairman on the steering committee for ICOR, which you've heard briefly about.

MS. McCOLLISTER-SLIPP: Hi there. My name is Anna McCollister-Slipp, and I am a co-founder of a company that does health data analytics called Galileo Analytics, but I'm here today as a Type 1 diabetes patient and patient advocate.

MS. PAXTON: Hi. I'm Liz Paxton. I'm the Director of the National Implant Registries at Kaiser Permanente.

DR. KUNTZ: Good morning. I'm Rick Kuntz. I'm the cardiologist and chief scientific regulatory officer for Medtronic.

DR. DANIEL: Thank you.

So, Rick, I think you're first up. Do you have slides?

DR. KUNTZ: Yeah, I do. I'm going to make a case that registries

are good, which is a pretty -- kind of a cheap shot. And, this is not necessarily an industry perspective. It's a perspective of me being in industry, so take that perspective.

Given the fact that we're talking about registries with a special emphasis on surveillance, I think at least from my perspective I'm going to keep pace with what's going on in the environment and increasing demands for clinical evidence. There are a variety of efforts that have tried to capsulize what's going on in evidence and this is from the IOM Learning What Works.

A shift from efficacy to effectiveness is occurring dramatically as we start to realize that the integration of healthcare systems average operators patient outcomes are just as important, if not more important, than a more specific focus on an efficacy endpoint.

We have to understand that the models for clinical research based on a point in time to do a randomized controlled study testing on a hypothesis with time for follow-up analysis and then the average two years to publication is not keeping pace with the opportunities in technology to advance patient care. We have to understand that there are a lot of small studies that need to be aggregated, and there have to be technologies and advanced methodologies -- to both look at the collective wisdom from those studies as well as leverage those studies in follow-up.

Our classic comparisons in the past have been with placebo,

and these are of less interest to patients than comparing to real alternatives, so the desire to drive comparison with other outcomes is something I think we're seeing more shift to. A focus on the patient unique characteristics rather than extrapolating the average patient effect from a randomized controlled study is of great interest, and that obviously has both statistical and sample size challenges. And, our ability to expand analyses, I think, dramatically increased over the last 10 or so years, especially in the observational arena, and an ability to take observational studies and move them into a more controlled environment, especially with respect to confounding.

Meanwhile, we are moving from a paternal framework where all you have to do is make the physician happy to understanding actually there are a lot of people that need to understand data who are in the continuum of care. So, this broader stakeholdership is now all demanding data, as they should, and they demand data in a language that they can understand. But they're equal partners in understanding how to make these decisions going forward, so these are increasing the volume of evidence required in order to satisfy those people who deserve to make decisions.

And, then, finally, dissemination and uptake is an actual specialty inside, in and of itself. How do you distribute the knowledge from studies so that people can make informed decisions? All of these are critical environmental issues we have to consider when choosing what type of format

or research to do going forward.

We look at the randomized controlled study, clearly the gold standard for validity. The capability of randomization to control confounding is unparalleled, but there are some limitations of RCTs that we know. It's highly valid, but they are narrow applications. It's generally powered for specific hypothesis tests. Most people don't pay attention to the secondary analyses and multiplicity. Inferences based on the average sample effect in general is poorly generalizable.

And, that's mainly because the screening requirement to get patients who actually can perform the duties required to participate in the study limit the kind of generalizability that can be obtained, including the hospitals that can do studies. And, they're large and expensive and certainly not scalable. There are minimal economies of scale, and there's obviously an increased demand that just won't be satisfied by these one-off, build the tent up, do the study, and take the tent down randomized controlled models.

For example, in our company, which has over 350 product lines, over 10,000 different products, here's one product: a coronary drug-eluting stent. In this most recent study, 5,400 patients were followed for five years. Its predecessor had 24,000 patients followed for five years. And, those were all the studies that were done, almost all of them randomized controlled studies that cost well over a couple hundred million dollars.

If we look at the expenses in a company like ours, which is

going to spend about $400 million in clinical research, the compound annual growth rate in clinical research especially in the postmarket requirement has gone to an unsustainable rate. We're seeing anywhere between a 25 and 50% increase in clinical research costs depending on how you break it down. In the postmarket we're seeing almost 100% annual increase in the cost of doing studies globally in the postmarket. Since we're anchored generally in the randomized controlled study arena, this is just not a sustainable model.

What about large simple trials? This is something that has been around for a long time, recognized it has not been applied as much as it should, and there are great studies in the past, ISIS, GUSTO, and others, that have been fantastic examples of cheaper, more scalable research studies. They address issues of RCT inefficiency. They generalize -- they use large sample sizes. They focus on ease of use, and they require minimal administrative oversight. And, there's a hope and a potential for these to be dropped into the electronic health network framework, if you can get past a few small hurdles, including ease of consent.

But, in general, they're not optimum for complex endpoints or special device application. The requirements for large simple trials really are unambiguous endpoints that don't have to be adjudicated -- very common treatments or conditions. And, when we're looking at the specificity of device application, this is probably not a readily available solution. There are going to be some examples, but not what we can count on.

So what about registry methodologies? And, by the way, I'm interested in the word "register." In the U.K. they call them registers. In the U.S. we call them registries. And, I was informed by somebody from Oxford that a register is one study, a registry is a collection of registers, just to let people know. We'll be talking about registers for the next two days. And, I don't know if that's true or not. Maybe we can get some other comments.

In general, they're better with respect to generalizability at the cost of less validity, and they're broadly applied. There's been profound improvements in confounding control. The general application of some tools, such as propensities for adjustment, instrumental variables, better attention to complete ascertainment has been something that's happened a lot more in the last few years, and we're starting to see some true fruit from the register format, which in the past was equating itself to kind of sloppy studies. It certainly offers a more scalable and reasonable cost-efficient platform and offers live data analysis for quick application and results and incorporates much easier with clinical management systems, I think, than the randomized controlled studies.

You'll hear, I think today, obviously, about the reports and registries HRQ and Outcomes research has done, so we have a variety of really good documents that are up-to-date demonstrating the real values and applications of registers. And, in general, they are just multi-purpose devices to be able to accumulate data over time with the caveat that they have to --

you'd have to consider selection bias, and it has to require tools for correction of confounding.

There are lots of examples of registers that have been very, very helpful in the past. This is again from the AHRQ document just outlining some real winners, and we all know them. The question is can these be applied in longitudinal follow-up in clinical and devices per se? If I put my PCORI hat on, our methodology committee has also developed a report in May of this year outlining state of the art clinical research methodologies, and they have their own chapter on data registries and what the reports are. So, we certainly have enough up-to-date information about what the elements are of registries and how do to them correctly.

Here's an example of a study done by Drs. Mori and Norman in internal medicine a couple years ago leveraging the register from the state of Massachusetts on the cardiac outcomes study. And, this is a study meant to address issues of quality of both devices and also operators, but from this data they were able to leverage information to address the question are drug-eluting stents of value in the treatment of acute myocardial infarction? And, this passed the gauntlet in internal medicine and has been a pretty valuable piece of information demonstrating that DESs have value.

We also want to pay attention to the learning healthcare systems, which is I think maybe more than just a new buzzword, but how do patients actually interact with the data on a regular basis. And, we have to

consider in trying to understand how to put together a platform of research for devices that interacts and extols some of the virtues outlined here in learning healthcare systems, but mainly an interactive system that can apply more readily available data over kind of a natural history and the real world environment.

Here's an example of that. We had a PCORI conference at Stanford a couple months ago. The C3N run by Peter Margolis in Cincinnati is an outstanding social network of clinical research that's really a community-based system based on hospitals and clinics addressing mainly the problem of inflammatory bowel disease in children and has been an outstanding learning system that has generated publications. It's low cost economies of scale and has been great and has generated the value of collection of clinics and registers over time to develop the network-based production concept.

What do we need in surveillance? We need to measure better device performance and confirm efficacy. We need to demonstrate long-term efficacy, which is not available from premarket studies. We need to show its effectiveness.

So we take these devices that have been studied in a selected group, how they perform with average healthcare systems or different healthcare systems, how they perform with average operators, and when they finally get distributed, what is their broadened application going to be? Do they require more studies if they become -- on the areas that don't have

clinical evidence? And, with time we'll start to understand the real outcomes patients are interested in.

And, what about comparative effectiveness? Again, most preclinical studies are generally done against either an existing comparator, which is a like device, but often patients want to know how they compare against other real alternatives that they have. And, then, only in large sample sizes can you come up with the power to detect rare events. And, what are those rare events? How do you detect them? How do you determine whether a rare event is happening too often? Is it predictable and can they serve -- are there machine failure points of conservative surrogacies for clinical endpoints?

If I look at the total product life cycle from our perspective in industry, on the bottom we have what we do from industry perspective. We try to design a product on the bench. We do some premarket pivotal and pilot studies. We go to the update panel and the data gets evaluated, and then the device gets thrown on the transom and then it gets used in the market. Only recently have we paid attention to the fact that actually after it's approved, it's really important, that study as well, postmarket studies and surveillance. And, then we consider those issues of weaknesses of the device as it performs as the input for specs for the next cycle of design.

The way to study them is on the top. And, so we generally study the premarket step with both computational modeling and a variety of

other techniques used in engineering and then slowly move into the clinical arena, but generally stop at the pinnacle of the study, which is the premarket study. And, then the follow-up has a been a hodgepodge of a variety of different small registers, some of which are not well designed, and good studies if mandated by the Food and Drug Administration.

In looking at how one can try to study these, one has to consider all of the different variables that occur -- levels, what the different endpoints are of interest. Early on we're not looking at clinical endpoints. We're looking at design specs, and we're looking at minimal variation and lean sigma approaches. As we move into the framework to the right, we start to get into patient variation in outcomes. And, these all require different methodologies of research.

What about using the device surveillance model for using the register process? If we look at how they've been performed in the past, I'll show you the different levels of efficacy, but I want to point out a couple elements that are critical.

In looking in the register to capture what happens in the postmarket to be able to keep pace with the total product life cycle, one has to understand how did you capture the patient? What was the follow-up methodology? How specific were you at endpoint? How high was the ascertainment follow-up? Did you have missing data? And, what was the source for inference? And, so I have two slides here just grading where I

think the kind of models have been for surveillance.

The lowest level of validity I think is the existing model of the MAUDE database, which has a pretty minimal understanding of how the data was captured because it's all voluntary. The follow-up has generally been passive, but the data specificity is high. This is a really good database for qualitative analysis about product failure and return product analysis, but generally a poor methodology to assess rates. It doesn't cost much. It's very qualitative, but the rates are not really useable.

The next level would to have a more active follow-up system with still no control over patient entry point. This would be like looking at the national debt index with a special endpoint that you can look at, per se. You might be able to get a rate if you can get an understanding of what the denominator is, but it doesn't have much specificity.

Most device registries really are the next level, which is a low level patient capture. Again, people don't pay attention to how they actually get into what the intake methodology is. The follow-up is generally active. You usually pay sites to do the follow-up, and their specificity is high. The rates are somewhat biased, but they're still poor inference because we don't know the patient population.

A more leveraged approach is to have a network that has a full understanding about how patients are captured. For example, to make sure you're going to make inference on whether they get consented. You have

active follow-up, high data specificity, and these are the special networks, the kinds that we're trying to do in my company where we specifically focus on devices with registries and fields directed at the endpoints of those devices. Still somewhat low cost, a little bit leverageable, but moving the right direction.

The more desirable ones would be where we utilized full electronic health records from single payer systems like the U.K. CPRD's data, or on top of that a dataset that has register elements on top of the HRs like the National Health Service U.K. National Joint Registry, which I think is probably the best in class and very similar I think to the Australian registry, where there's actually an effort to leverage existing data on electronic health records so there's no missing data. We understand where the patients came from, and there's specificity with them on top. And, this is I think where we want to go going forward.

We need to pay attention to the fact that the clinical endpoints are critical. In devices, you need high specificity. It's not easy to use just the HRs alone. Device circuit endpoints I think is something we have to pay attention to. How do we measure machine failure issues before they actually cause endpoints in patients? Like changes in impedance in a high power lead in an ICD generally predicts fracture of that lead.

We have to be able to understand how to detect adverse events and make inference on them. I think like the DELTA system-- have

good analytical oversight that's independent. This is critical because we can't have industry doing all of the analytical oversight. We don't want the liability, and we need better objectivity. And, then the reporting structure is critical. How do we get that data out to people who are going to use the information going forward?

So, I think the answer is that the registry platform is likely the best platform for device surveillance. The desire for frequent monitoring exists to take appropriate action and provide rapid design feedback. That really fits in well with this framework. And, the monitoring and decision making for device events are not well worked out under the registry platform at this point, and we have to work through a variety of different -- of issues about how you look at continuous monitoring because as the manufacturer I want to monitor that dataset every second and find out when something happens. And, there are some challenges in data analysis in that arena.

In conclusion, medical therapy surveillance is presently suboptimal across the globe. We all know that. That's why we're here. The growing concept of outcomes research with emphasis on developing networks up to scale with an observational research system will provide the basis for responsible medical device research in the future. Proper surveillance research requires serious attention to design and statistical elements in order to provide useable results to improve healthcare for all stakeholders.

And, finally, there are great opportunities presently to improve global healthcare by leading and pioneering novel methodologies in medical therapy surveillance. And, I'll stop there. Thank you.

(Applause.)

DR. DANIEL: Thank you, Rick.

The next speaker is Marissa.

DR. MILLER: Good morning, and thank you to the organizers for this invitation to be here and be part of this dialogue. What I'd like to do is first put into context registries in the context of NHLBI and NIH research. And, then I want to go into several examples that hopefully will illustrate some points I'd like to make.

NIH oversees scientific investigations and biomedical research, and they're laid out in three main areas: basic, clinical, and translational. Registries fall across these three domains. And, depending on sort of the impetus and how the issues come to NIH depends on whether we actually will support a registry or not. We do this selectively, especially at the National Heart, Lung and Blood Institute.

So the three basic registries that have been initiated in the cardiovascular realm that I think will illustrate some of the points I'd like to make are the Percutaneous Transluminal Coronary Angioplasty registry, which evolved into the dynamic evaluation of percutaneous interventions, the GenTAC registry, which looks at genetic, thoracic, aortic aneurysm and

other cardiovascular complications, and INTERMACS.

And, very briefly, the PTCA was initiated by NHLBI after the very first angioplasty was conducted in 1977. It started as an NHLBI form collection, evolved into a contract looking at many, many sites that were utilizing this new technology, and soon became a more focused registry collecting data from 16 sites. Again, this technology was evolving very rapidly. There was an interest in looking at patient outcomes. And, up until -- many outcomes came out of this including the morphology of plaque, how to utilize balloons and guided wires in the procedure, and so forth. The motivation was very much on the clinical outcomes of patients and scientific investigations.

GenTAC also came about because the scientific community approached the NHLBI with an interest in the genetic basis for these diseases. It was believed that a repository of biological samples along with clinical information on patients would advance the field very rapidly, and this is in its second iteration. Again, it's very much focused on genetics, imaging, and clinical outcomes of patients.

INTERMACS, which is the Interagency Registry for Mechanically Assisted Circulatory Support, probably is the best example of what we're talking about here, which was an impetus from NHLBI. The Institute of Medicine in its report in 1991, after the total artificial heart was launched, initially said that because patients are fully dependent on this technology,

they should be followed for their lifetime. And, that was really the marching orders that the National Heart, Lung and Blood Institute received. I think there are some unique attributes to INTERMACS that should be considered in the development of new registries and that allows the utilization across many domains and not just the research domain.

Just basically lots of you who have been here this week have heard about INTERMACS. I'll try not to repeat too much, but it's a national registry for patients receiving durable approved ventricular assist devices. It's focused on adults. We're expanding into pediatrics. We're expanding internationally as well. And, again, in support of the NIH mission to advance the understanding of this new technology to improve health, to advance the development of new devices, and hopefully inform future decision making both in terms of research and in terms of regulatory activities.

So you've probably seen this slide before if you've come to any of our meetings or last week or even yesterday with David Naftel. What's been unique in the development of INTERMACS that's I think instructive as we move forward is from the very beginning, even though initially this was funded by NHLBI, the way this was constructed is that all of the stakeholders were at the table at the very beginning. That included the three collaborating agencies, the NHLBI, the Food and Drug Administration, and CMS, but also our industry partners and clinicians and academicians.

So the very first year of the development of this registry

involved hands-on monthly meetings with all stakeholders at the table defining the data elements, the data definitions with input from the regulatory and reimbursing agencies. So as we move forward, all these interests were integrated into the registry that has continued over the course of this registry and has really enabled us to have a sustainability plan and process whereby these entities all now pay in and we have a long-term path for the registry.

You've probably also may have seen this slide, and the previous speaker really brought through many of these points. I think the highest level of evidence in making most any decisions is the randomized clinical trial. There are drawbacks to that. I think as we move forward with registries -- and the AHRQ second edition book speaks to this -- we have to think about the quality and rigor of our data and the extensiveness of the data. Registries do allow for collection of information on patients far beyond what a randomized clinical trial allows. We are going on 8,000 patients in the INTERMACS database now with over 400 elements for each patient.

But at the same time we have to make sure that we have rigorous inclusion/exclusion criteria. Our adverse event definitions are evolving along with the thinking of FDA, which I think is important. We are able in this registry to collect in excess of 85% of all of the durable approved devices going into patients, and we have, because of our collaboration with industry, an idea of the denominator, which allows very accurate rates to be

assessed. Anyway, if you build in these rigorous aspects, you have quality data that can be used across the spectrum from research to regulation to reimbursement decisions.

Just in summary, and again instructive for the broader discussion, having that upfront cooperation and collaboration across entities to assure that many needs can be met, I think, is critical. Having some kind of national relevance in size and extent so that what you're looking at is reflective of what's going on in that clinical area, device area is important. Having FDA as a full partner, obviously if industry is going to utilize your registry in terms of either pre- or postmarket activities, there has to be that ongoing dialogue.

And, I think that building a rigorous platform that it can then be leveraged in many different ways is also very important in this period of constrained budgets, particularly with what's going to hit us very soon in the federal government. So when you have a platform upon which you can build substudies, you can develop hypotheses for additional investigations, even launch clinical trials, I think registries are a phenomenal platform for that. Obviously the challenges include maintaining the rigor and the high quality and as I mentioned the sustainability.

So the lessons learned in terms of NHLBI's involvement in registries is again to have the stakeholders at the table in the planning phases, to integrate all of the interests of the various entities up front as you

design the registry and conduct the registry, provide a conceptual pathway for collaborations, again, to leverage your infrastructure and make the most use of your investment, and then plan for your long-term sustainability. And, again, the more rigorous your data, the more complete your data, the more likely people will ultimately pay for your data, so that's very helpful.

So in terms of NHLBI's goals and priorities for the future, our short-term goal is we're kind of -- I think in some ways we've been considered a bit ancillary in terms of some of the registry activities that have gone on. And, we would like to try to work with the societies and others that are stepping forward in terms of the medical device arena to consider the research needs and research opportunities, and we're in the process of doing that.

We want to assure in terms of INTERMACS specifically -- and we're working very closely with FDA -- that our registry will continue to provide data that are needed for evaluation of adverse events, for evaluation of pre- and postmarketing activities, and to have that broad discussion across all the stakeholders as we move forward. And the beauty of registries, again reiterating a point that was made previously, is we have the opportunity to adjust and be flexible as both the research environment and the regulatory environment changes over time.

Because the NIH is under the common rule, we have some restrictions in terms of human subjects issues and approaches and informed

consent and other issues that have been -- that must be addressed sometimes do impact our efficiency and our ability to get to all the patients we'd like to. Again, we're looking at how other registries are navigating this pathway in terms of how we go forward. And, that's a very big concern of ours currently.

And, long-term goals, we want to again do this comparison between what registries can do and provide and our randomized clinical trials that tend to be much more expensive and see if registries over time can fill a bit of a void and a gap and also be a more cost-effective means of doing research, posing research questions, as well as providing all of the other benefits that I've already mentioned.

We also are watching very carefully the FDA experiment that Danica has described, and we very much want to be a partner with FDA as you move forward in terms of research questions that can be built in, new methodologies, new approaches, and new partnerships. So thank you very much.

(Applause.)

DR. DANIEL: Thank you, Marissa.

Our next speaker is Elise Berliner.

DR. BERLINER: Hi. I don't have any slides, so I just wanted to maybe bring in a little bit of a different perspective. I guess I wouldn't say that it's an either/or situation for randomized controlled trials and

observational studies. I just want to remind everyone that observation is a key part of the scientific method -- that the scientific method starts with making an observation. When you measure some outcome in a patient, the patient definitely experienced that outcome.

The question that we're trying to figure out is: why? And, that whole hypothesis generation thing, it's really important. And, at AHRQ we do a lot of systematic review, and we've looked at thousands and we've looked at thousands and thousands of randomized controlled trials, and a lot of times they don't have the answer. And, a lot of times the reason they don't have the answer is because they were not designed using the appropriate hypothesis, so they have the wrong comparator, they were not powered adequately, and we really need observational data as a critical part of the scientific method.

But another thing I wanted to say is that I really applaud FDA for trying to put these postmarket and MDEpiNet and all these initiatives into the broader public health context because another thing we're realizing at AHRQ is that it's really critical to pool resources and work together, that no one entity is ever going to have enough money to collect enough data to answer all the questions that we need to answer.

An example of that -- yesterday we were talking about the different pacemaker leads, so at some point you might have enough data to say that one lead is significantly worse than another lead. And, so, the FDA

might have enough data to take action or the company itself might decide that they want to pull it off the market or redesign it, but there's still lots of patients that have those leads in their body, and they need to know what to do.

We need to keep studying it beyond -- the FDA might be done doing what they need to do, but from a public health point of view, there are still lots of patients that are going to be asking what do I do? Do I take it out? Do I replace it? What do I do? That's sort of the background. We have this huge pace of change of technology, but we still have this duty to patients to study.

And, another -- just to comment on some of the conversations we were having the other day, so we are looking at different sources of data and how to combine those data, and that's absolutely critical. But there is also -- we are also going to need new data, and people mentioned getting data directly from patients. And, an example of that is, AHRQ is funding together with the NIH and with the ACC and with industry a longitudinal study on implantable cardiac defibrillators.

And, this study has turned out to be much more expensive than I would have thought considering that we're just taking existing data sources, which are data from the NCDR and data from the HMO research network, and then we are doing some adjudication of the shock data from the ICDs themselves. And so, just looking at that whether the shocks are appropriate

or inappropriate, it's ending up to cost a lot of money.

But we just published a systematic review on another issue related to ICDs, which is that there were some guidelines published recently that physicians should have conversations with patients before the ICDs are implanted about what happens at the end of life, so that eventually should these devices be deactivated at the end of life. And, there is no evidence on how this conversation should happen, when this time comes, whether doctors have the information from that conversation, whether patients still have the same feelings about it at that time, and those questions are all critical to answer. So how can we add in questions into existing data infrastructures instead of starting all over again? I think that that's really the challenge that we're facing.

As far as what AHRQ is doing, I was very happy to hear already this morning two references to the AHRQ User's Guide. I have to definitely point to my colleague Rosemarie Hakim from CMS. The whole guide was her idea. And, we are just so happy to see that people really find it useful. The purpose was to have a how-to guide to help maximize investments in registries and make the data as valid and reliable as possible, as Marissa said.

I also just want to point out to everyone that the third edition will be posted in the next few weeks, the draft for public comment, so we definitely invite everyone to look at the AHRQ website and read the draft and comment, and we would be happy to incorporate everybody's comments.

Some of the interesting trends over time in the registries handbook as we're moving on to the third edition, which I think are the themes that we're really discussing in this meeting, that the important issues that are the real cutting edge issues in registry are the issues of how do we link data sources and the legal and ethical issues, patient privacy, informed consent, the protection of data from discovery in litigation, that those are the kinds of issues that people are really concerned about, and that in order to make this whole thing work, those are the really critical issues that we need to solve.

The other really big initiative at AHRQ is to do all the registry of patient registries or registers, but that will be a registry of registries, so I can use the word registry. And, we want to create a place to find information on existing registries, so if someone wanted to study some clinical question instead of starting all over again, could they partner with someone that already is collecting data on a similar question?

We're coordinating with clinicaltrials.gov. Clinicaltrials.gov already collects information on observational studies, and there are already about a thousand things are identified as registries in clinicaltrials.gov, but we are adding in data elements that will be useful really for this question of how can the data be leveraged and utilized by others? So for people who want to make partnerships and really collaborate, that's really where we're trying to go. I want to point out that it'll be totally voluntary registration, but we do

hope that everybody will find it useful and will take the time to register their registries and also to use it as a resource.

And then, one of the most interesting things, part of this project is what we call the outcome measures framework. And we discussed this a little bit yesterday too, that one critical issue is that studies all use different definitions for outcome measures. So they might use different definitions using the same words, or they might use different words, and they really mean the same thing.

So how could we develop some sort of standard data dictionary so that people can put into the system what their definitions are, and then the next person who puts in their registry can say whether they used the same definition or a different definition. And, it's actually really, really difficult to do that. I think that that's something that probably it won't be implemented in the first edition of the registry of patient registries, but something that we're going to have to work on over the next few years.

And so, just to end up I also want to say that AHRQ is funding specific registries. We're funding the FORCE-TJR orthopedic registry, which Pat, my colleague Pat Franklin who's the PI, will be talking about that later today. We're funding a glaucoma registry. We're funding a lot of other specific registries, so we're asking the same question that FDA is asking. How do we find partners? What's the value proposition for keeping these things going? How can we integrate these registries with other initiatives that are

going on? And, I think that those are the critical questions to address over the next two days, so thank you.

(Applause.)

DR. DANIEL: Great. Thank you, Elise.

Our next speaker is Elizabeth Paxton.

MS. PAXTON: First of all, I'd like to thank the FDA for the opportunity to share our experience at Kaiser Permanente with device registries. At Kaiser Permanente over the past 10 years, we have developed five orthopedic, three cardiac, and a vascular stent registry. We're currently monitoring over 300,000 implants on a longitudinal basis.

These registries were initially developed after the Swedish national registry for hips and consist primarily of standardized documentation. Our physicians came to consensus in terms of data elements that would be collected preoperatively, intraoperatively, and at each follow-up. This allowed us to collect information on patient characteristics, surgical techniques and implants, and outcomes with revision as the primary endpoint.

In addition to these standardized forms, we also have access to information in our electronic health record. We're able to match this information with pharmacy, lab, imaging, and utilization data to provide a very comprehensive device surveillance mechanism.

One of the unique features of our registries is the quality

control. We validate the procedures, diagnostic codes, and implants using independent databases, and we also conduct a thorough chart review of each outcome using our electronic health record.

Another unique feature of our registry is our dynamic feedback mechanism. We provide feedback to the frontline staff and physicians through numerous mechanisms, including meetings. We work very closely with the chief's groups. We have site visits to the different medical centers. We have an internal conference as well as present at external conferences. We have an annual report that's provided to all of the physicians and staff. We also have newsletters that are provided on a frequent basis. And then I'll share some additional web-based tools that we have used to disseminate information.

How have we used this information at Kaiser Permanente? Well, first of all, the registries have been crucial for patient safety in regards to recalls and advisories. We've had numerous recalls where we're able to identify which patient has that implant, immediately notify the physician and the patient, and monitor that patient on an ongoing basis to ensure that they receive the follow-up care that is necessary.

In addition to patient safety, we also use the registries for quality improvement efforts. The registries allow us to evaluate longitudinal outcomes of devices so we're able to determine what are our revision rates, what are our re-operation rates, and monitor that over time.

In addition, we can look at different implants and compare their effectiveness. This is an example from our ACL registry, in which we looked at different types of grafts and found the allograft type was performing at a lower level. This information is then fed back to our physicians to influence the clinical practice.

Another way that we look at data and use the information at Kaiser Permanente is identifying risk factors associated with revisions and complications. This is an example of revision risk factors associated with total hips in which we found the femoral head size in metal on conventional devices were at higher risk for revision.

We also are very involved with our quality improvement programs at Kaiser. We have ongoing monitoring of our complications on a quarterly basis. And, this allows us to detect early problems associated with devices or at certain medical centers. So, this is provided not only to our chief's groups, but to our quality departments and also to our risk managers.

In addition, we have medical center specific reports that are provided using our web-based system as well as providing specific information. And, this allows us to compare each medical center with the region as well as nationally, providing some benchmarking information for quality improvement.

In addition, we identify centers that have higher than expected revision rates or complication rates and work closely with the chief's groups

to identify the underlying source of that variation. This is an example of a specific center that had a lower survival when it came to looking at total joints. And, we had an independent surgeon work with that center to identify the cause of that particular issue and provide a feedback to those physicians for enhancing the quality of care.

We also have surgeon profile reports that we provide. And, this allows surgeons to look at their demographics, the types of implants they're using and their outcomes in comparison to their medical center, the region and nationwide. Physicians who identify higher revision rates can then work with us in order to identify the underlying source of that particular issue.

Another way that we work with our registry is through revision risk calculators. This provides an opportunity for the surgeons and the patients to work together and identify risk of complications and revisions before the decision of treatment is made. So, this is information that can be gathered from the patients, such as the gender, BMI, enter it in this risk calculator, and their risk of revision is immediately identified for clinical decision making.

How does this influence our clinical practice? This is an example of some changes with head size associated with registry findings. So the registry findings have impacted our clinical decision making along with existing information in the literature. This is another example of our

reduction in revision burden and revision rates for total hips as a result of both the registry and other available evidence.

What are our keys to success? First of all, there has been physician involvement in all stages of the registry, and that's been the most important factor in the success of our registries. The registries also have to be minimal in terms of burden to the frontline staff and physicians. Another important factor has been providing direct feedback to the clinicians and staff so they're aware of how this information is being used. We also have taken advantage of the numerous existing databases within our system to enhance the data collection. And, another key to success has been our rigorous quality control mechanisms and validation of our outcomes for high quality data.

For the future we are looking at integrating the registry more into our workflow with registry modules and more of a bi-directional aspect with our electronic health record. We're also looking at taking advantage of clinical decision tools and reminders. We're looking at different mechanisms for automated postmarket surveillance for adverse event detection. And, we're focusing on the patients with virtual visits as well as collecting patient-reported outcomes.

And then, finally, we're looking to collaborating with the FDA on national efforts as well as international efforts such as ICOR. Thank you

(Applause.)

DR. DANIEL: Great. Thank you, Elizabeth.

Our next speaker is Nancy Dreyer.

DR. DREYER: Thanks very much. I'm happy to be here and particularly delighted with the assignment of this particular talk, so if it ever comes up I'll -- I'm talking to you about governance and data access.

We've heard some fabulous descriptions of important registries and tools that really make a difference, but what I'm going to talk about I think is critical to the success of any one of these registries and one of the more under-appreciated aspects of planning successful collaborations.

We're talking about governance, how you run things, data access, which is who can use the data when and for what? It seems straightforward, I'm sure. But I want to talk to you about some principles of just governance. It's critically important to start with a plan, preferably a written plan. What is the charge of the governance council?

For many of you who are experienced researchers, I'm sure that like me you share the wounds and the war stories of ineffective governance and projects that had the best of intentions and went terribly wrong because of things that could have been clarified if you'd declared them at the outset.

So the role of the advisors -- on this slide you see some of the examples of things that they're often asked to do.

The membership is important, so we always like to include key

contributors, key stakeholders, but that's too simple. How long are they on the board? Do they rotate? Do you include methodologists who guide things but perhaps are not direct contributors? We see more and more programs where there is an important role for a patient advocate who serves the position of keeping it real and keeping it focused, which sometimes gets lost.

And, then the process. Will you be voting? What kind of vote does it take to pass something? Where do the sponsors fit in? Do they get to vote? Do they get to just chat?

And, the last but extremely important is how do the meetings get memorialized? I mean whoever writes the history dictates what gets remembered. And, if you've participated in these kind of meetings, you know that many things are discussed, but how they're memorialized often doesn't really represent what you remember happening as the most important things. So, it's an extremely important aspect.

I'm not going to describe INTERMACS again because we heard a fabulous overview of it. But, what I wanted to show you was a little bit about the governance. Look at this. Look at all these committees. These are all the stakeholders that are involved in this process that Dr. Miller described this morning. And, the fact that they have a well-established governance process which gives a voice to all the stakeholders and keeps them involved, maintains their interest, this is I believe a key reason why they have been able to generate as much value and sustainability as they've had.

And, I do want to draw attention, since our registry handbook sponsor is here, that this is described in the 2013 edition of the handbook in a new chapter on public-private partnerships, which will be up for public comment in a few weeks.

Just a few points that I've learned both from personal experience and from participating in the handbook is the importance of choosing the chair. It may sound trivial, but you need a respected leader who can unite parties, drive consensus. This is a hard job for beginners. It's much better to have experience. And, you do need to clarify their role at the outset. They may have their hand in everything, but are they a co-author, a lead author? What is that role?

You also need to plan for dispute resolution. I know where you always start these, we're all one big, happy family; we all get along because we have the same purpose. It is inevitable that there will be disputes, and you need to plan for them and plan how to get out of them. I've had disgruntled authors come in and say, well, I'm a collaborator. If you don't do it my way, I'm withdrawing all my data from the study. You have collaborators who say they're not satisfied infinitely on manuscripts. These are important processes.

And, finally, you need to prepare for transparency and act in a transparent method. This is not an old folks club, old boys club, girls club that you can act behind closed doors and just make decisions. That doesn't work

anymore.

If we get past, that let's just talk for a moment about data access and planning. You know the principles are fairness. Easier said than done. Who gets the first crack at good ideas? It's amazing how many people claim responsibility for a great idea and that they should lead it. How do you balance the roles of registry contributors? Do they get preferential access to the data? What happens when outsiders want it? How do you apportion authorship? It's important, and people care about that. And, if you have a plan, then it will work.

And, of course, it's important to think about the regulatory and legal responsibilities because part of acquiring data is the responsibility to report it, and as we also heard this morning to protect it from irresponsible use and also to deal with unintended aspects like litigation that we heard about.

For data access just like governance, expect the best, plan for the worst. Data management needs to talk about, of course, protecting the identities of patients and physicians and any confidential sponsor information. But, the documentation particularly from observational studies is particularly important. We heard Dr. Berliner talk about the outcome measures framework. People will often hear about your study and assume they understand what your measures are when, in fact, particularly in observational research it's critical to be very clear about describing that and

making sure everybody understands it.

And, then a key question is who does the analysis? Not just from a turf perspective, but for guaranteeing the quality and that things are done right and so you can stand by them. So, will you do it all centrally under various people's directions, or will you send out datasets?

And, then the key question is how do you safeguard quality? Is there a central review? Is it binding? Non-binding? How can you assure appropriate use of an interpretation?

And, possibly the last bullet on this slide is one that should keep you up nights because the question is in a collaborative program, do you need to speak with one voice? And, whose voice is that? So, it's tremendously challenging.

My second to last example is the National Registry for Myocardial Infarction, which we call NRMI, sponsored by Genentech. And, I want to call your attention to this great publication in *Lancet* in August -- I'm sorry, in *JAMA* in August. This registry ran for 17 years, a huge program, lots of publications and abstracts, and as we've been hearing this morning made a tremendous difference in the treatment of patients. But, how did they do this?

They had an effective governance committee. Their advisory board had a budget. It's real simple. They got to do three publications a year. And, what they did is vet all the ideas and chose what they thought

were the most meaningful. That self-regulation strategy seemed to be a very effective strategy for producing scientific, high-quality publications. Now, that's not the only what, but it was an interesting model that I wanted to offer you.

It may seem straightforward to think about these things, but truly the devil is in the detail. But, if you think about them, you will have the possibility for a very successful program. Thank you.

(Applause.)

DR. DANIEL: Great. Thank you, Nancy.

Our next speaker is Michael Mack.

DR. MACK: Thank you, Greg. And, I'm here to tell you we are living every single aspect that Nancy just mentioned in her presentation there. You're right. The devil is in the details. It didn't sound easy to begin with, but looking at this some days is a nightmare. This is the wrong talk. Could I have my other talk, please?

This talk is successful partnerships for registries development. This was an editorial by Bob Hauser in the *New England Journal* in February of this year. "Professional societies, the medical device industry, and the FDA should mobilize available resources now to improve postmarketing surveillance for these patients. Otherwise, no doubt we will be here again." And, this was discussing ICD leads.

And, at that time what was being generated was the STS/ACC

TVT Registry. So, what it is is a new outcomes registry of transcatheter aortic valve replacement that was approved -- which is a device that was approved in the United States in November of 2011. The registry currently has greater than 400 data elements. It's a web-based data entry. There are standardized data elements based upon the Valve Academic Research Consortium definitions. There are 30-day risk adjusted clinical outcomes. It will be linked to CMS data so that we'll be able to have long-term outcomes and will be harmonized with the STS database, which captures 96% of aortic valve operations done in the United States. So, ultimately we'll be able to perform comparative effectiveness research.

The vision behind this was the creation of a generic platform that would serve as an infrastructure for a premarket IDE device submission, postmarket surveillance, coverage with evidence development, and be generic for different devices and device iterations of the same devices. And, the idea was to develop a comprehensive infrastructure for disease management so that we could perform comparative effective analysis, cost effectiveness research, appropriateness of care analysis, quality monitoring, performance improvement opportunities, and observational and hypothesis-driven studies of real world practice.

The idea is traditionally registries have been here in the total lifecycle of a device, and the idea of this is to expand the role of a new generation of clinical registries into the postmarket and post-approval areas

and to the premarket arena.

So, these are the partners or the stakeholders in the TVT Registry enterprise. It's the Society of Thoracic Surgeons and the American College of Cardiology, along with the Duke Clinical Research Institute, both pre- and postmarket divisions of the FDA, CMS, NHLBI and Edwards Lifesciences, which is the sponsor of the only approved TAVR device in the United States at the current time.

The governance of this is there is a steering committee, and under the steering committee is the research and publications committee, which controls all data access to the registry, and a stakeholder advisory group. And, in the stakeholder advisory group are multiple different stakeholders, including other industrial partners who do not have a device approved in the United States yet, NHLBI, payers that are non-Medicare -- virtually all these devices are implanted in the Medicare population now and for the foreseeable future -- John Santa of *Consumer Reports* has agreed to participate in the stakeholder advisory group, patient representatives, the public healthcare system, and AHRQ.

This is the steering committee, which has four members of the STS and four members of the ACC. Many members of the steering committee are in the room today including Fred Edwards from the STS, Ralph Brindis from the ACC.

The registry operations are all done by the NCDR of the ACC.

Participating on the steering committee are Danica and Jamie Schaeffer from CMS, Frank Evans from NHLBI, and John Rumsfeld is the chair of the research and publications committee. All data analysis is done by DCRI, and Eric Peterson and Matt Brennan are the principals of that. And, there's a number of staff of both STS and ACC that are involved with the real work of the registry.

The timeline of this is the idea for this came in February of 2011 when the premarket section of the FDA approached the ACC and STS anticipating the approval of TAVR devices in the United States. In July of 2011 at an FDA expert advisory panel, the TVT Registry was proposed by the professional societies at that panel meeting. And, in November of 2011 -- so nine months after the idea of it -- the Edwards SAPIEN valve was approved in the United States, and the ACC and STS filed a request with CMS for a national coverage determination of transcatheter valves. And, then a month later the STS/ACC TVT Registry was launched.

In May CMS issued an NCD for transcatheter valves mandating participation in a national registry as a requisite for reimbursement. And, in July a web-based data entry portal was opened. This is the national coverage determination issued in May, which requires participation in a national registry, and the TVT Registry meets all the requirements of the NCD.

What are some of the innovative aspects of this registry? Well, first of all, it will capture all devices implanted in the United States. And the

reason for that is if you want to get paid for it, you've got to enter it into the TVT Registry. It will have the capability of incorporating UDIs. There will be immediate focus on critical issues, so this is real time, able to be queried, and have an immediate answer. So it is active surveillance.

Short-term risk-adjusted clinical outcomes will be able to be obtained and long-terms outcomes by linkage with CMS claims data. There also is quality of life outcomes data. This was mandated by the CMS NCD, so we will have one-year quality of life outcomes data available for this.

A risk prediction algorithm will be able to be generated once we have sufficient data within the registry. By linking with the STS, we will be able to have appropriateness of use assessment and comparative effectiveness. This also has the opportunity of being able to expand FDA label indications by IDE studies being nested within the registry. And, indeed, post-approval studies will be nested in the registry also.

The current status of it: as of yesterday there are now 106 actively enrolling sites in the United States. We don't know for sure how many sites are implanting in the United States, but there's probably about 170 right now, so we have over half the sites now actively participating, and we have now 510 patient records in this. Most of the ramp-up has occurred within the last couple of months. Again, it's not known how many devices have been implanted in the United States. Wall Street estimates are about 2,800 at the current time. And this is also serving as a nested registry for a

post-approval study for the Edwards SAPIEN valve.

Now, another of the issues -- how is all this funded? Well, the professional societies, the STS and ACC, have borne all the initial startup expenses associated with this. We had two large databases. We felt that this was a natural extension of our databases and it was the right thing to do. The ongoing expense has been funded by site initiation fees and annual participation fees, and funding has been received from Edwards Lifesciences for work that will be performed for the post-approval study.

What's the good and the bad of this? The good is that this is a new collaboration between many partners who have not necessarily worked together before, including the STS and ACC, which haven't always seen eye to eye on many things over the years. I think it establishes the capability for a more robust postmarket surveillance system than has been in place before. And, as I mentioned earlier, there's a significant expansion for the role of registries.

What's the bad? Well, right now it's a very burdensome data collection for the sites. It probably adds a full FTE to each site for data collection, entry, and maintenance. There was a lot of heartburn about the cost of the initial expense and the annual expense for participation in this registry from the study sites. Site agreements, contracts, and informed consent have been a lawyer's delight and nightmare for all of us trying to get the registry up and going.

And, communication between all stakeholders is a constant challenge in these uncharted waters. The communication has been -- there's weekly teleconference calls in which all stakeholders participate and been very diligent in, but there are so many side issues that come up and keeping everybody in the communication loop is a constant challenge. And, there's many things yet to be determined.

There's many stakeholders in this. This isn't just about postmarket surveillance, and different stakeholders have different goals. FDA needs a device to safe and effective, CMS needs it to be reasonable and necessary, and the professional societies are more interested in appropriate use criteria and guidelines generation from this. Can this be all things to all people? Or can it can be something that in trying to be this ends up not being too wieldy, too burdensome, and not very pretty to look at?

The next steps for the registry is we plan on having annual reports at the society meetings each year, so there'll be an annual data harvest. It will be linked with CMS data for long-term outcomes and will develop the risk model as I mentioned.

And my talk this afternoon will discuss the global harmonization of this registry with out of U.S. databases and registries. And, a lot of these already use common AHRQ definitions, so that the data dictionary is one of the things that's in place already that will help facilitate this.

We're in discussions right now using this for premarket use, so you'll have a common generic platform from device submission to the FDA for approval on through the total lifecycle of the device. And, then ultimately linking with the STS Adult Cardiac Surgery Database for comparative effectiveness with surgical AVR as this becomes more and more a commonly employed device.

In the national strategy, now where does this fit? Well, I think it fits right now in three different areas: the first is in post-approval studies; the second is enhanced postmarket surveillance; and then the third is building a national registry and the capability of interacting with international registries. Thank you.

(Applause.)

DR. DANIEL: Thank you, Michael. And you're right that was not a very good looking horse to look at, so -- or zebra. I don't know if that was a horse or a zebra.

DR. MACK: It's a zorse.

DR. DANIEL: Zorse? Okay. So our next speaker is Stephen Graves.

DR. GRAVES: Thank you very much. I'm going to try and give an international perspective on using registries. And, I guess that one of the things that's really -- what I would consider a registry is often quite different from what is being talked about today. I think a lot of the things that are

being talked about are really large observational studies or large clinical trials.

I would call registry something quite different, and that I think that a registry is not an observational study. It's not a clinical trial. What it is is a quality assurance mechanism that's been developed to monitor outcomes within a healthcare system. And, that healthcare system may be an integrated healthcare system, like Kaiser. And I think that Liz gave a very good explanation of how a registry is actually used.

But, it also can be scaled up, and it can be in large regions, or it can actually be -- and this is where I work and where many of my colleagues work -- a national registry where the data that we look at is everyone -- it's all-encompassing and that there's a number of features about registries which are actually quite critical in that the data that you get has to be validated from multiple sources and so that you know that it's actually correct. And, the very important aspect of registries is they feed back into the healthcare system so that you bring about change. And, you bring about change and you bring about that change very, very quickly. And, you can monitor what you do.

When you say something, you can actually immediately see the effect of what you say because the healthcare delivery will change. And, registries change healthcare delivery on a daily basis. Surgeons look at their own data and change their practices, governments look at the data and change pricing or remove devices from the market, companies look at their

data and make decisions about what they are going to do with the devices, whether they're going to add additional training or whether they should be using it in different centers. Hospitals compare their data so they compare it to each other.

What I'm talking about when I talk about a registry is something that is much more scalable than an observational study, and it's something that is actually integrated within the healthcare system to bring about change within that healthcare system.

Registries internationally have a long established track record. Liz mentioned that the Kaiser registry was based on the Swedish hip registry, but that wasn't actually the first of the device registries. The knee registry was, and that was established in the mid-'70s, and it's well over 30 years old. And, as I've mentioned the registries -- internationally the large registries are actually already integrated into the decision making of the healthcare system.

The relevance of registries. They are a quality assurance mechanism. They have broad-based community data which enhances the capacity of a wide range of stakeholders to use in evidence-based approach to ensure quality outcomes. For instance, with medical devices I wouldn't call an arthroplasty registry a medical device registry. I would call it a procedural registry. It looks at the outcome of hip replacements. It can monitor the outcome of devices.

And, I think the large registries that do monitor devices are in

fact the most effective postmarket surveillance tool, but they do other things. They actually also look at the outcomes of surgeons and hospitals. And, so it's a much broader thing that they look at. They look at patient factors, surgeon factors influencing the outcome. They provide data which is actually not available from any other source. Registries are also changing the paradigm in the nature and delivery of clinical evidence, and they provide real evidence in real time. And, there's an increasing expanding role for registries within healthcare systems.

What evidence do registries look at? They look at independent -- device comparative outcomes data. They identify best and worst practice. They simultaneously compare the effect of multiple factors on outcome. Through ongoing monitoring, they are sensitive to the impact on clinical change and independent quality information -- or it can provide independent quality information on a surgeon's own personal outcomes. Safety and outcomes data for industry and regulators -- that's one of their major activities. And, again, just to emphasize, it's real information in real time.

Despite the clear evidence from these large national registries, which has been established over many years, there is ongoing misunderstanding of the nature and role of registry data by those with little or no experience in the use of large registries.

This is one of the devices that the Australian registry identified

many years ago, and everyone is well aware of this. This was the ASR Conventional total hip replacement that we first identified back in 2008, but it took till 2011 before the device was withdrawn from the market. And, this was exceptionally different from other devices that were being used.

Here you can see the comparison at five years of the outcomes of the ASR with over almost 20% being revised at five years. The Australian is actually reporting on this device at seven years where over 40% have been revised. The revision rate should be about 4% at that time, so you can see it's a tenfold difference from other devices. So, they identify difference very, very easily.

The ongoing criticism of registry data is they are not clinical trials and therefore cannot be used to establish causality. They have not controlled for all factors, and therefore confounders would distort data interpretation. They are not Level I data. They cannot be used to compare prostheses. This is actually a quote from Biomet to a senate inquiry in Australia.

And, I've also got a quote from DePuy back in 2009, which is when we were reporting and discussing with the company about the problems with the ASR. And, what they said was that simple comparisons using registry safety data alone are not suitable for evaluating products that present a different risk/benefit profile, such as the use of conservative hips. Because as well as the conventional hip, we were also reporting the ASR

resurfacing was also an issue.

Now, DePuy has since come back significantly on that, but you see, these are the issues that we have dealt with over a number of years. And, fortunately what is actually happening is there is increased education that's going on, and there's an understanding that registries actually are protective of industry and they're protective of all the stakeholders because they are monitoring the outcome of healthcare delivery.

This is one of the classic things that is presented when discussing registries: the level of evidence. If we look at the level of evidence, clearly RCTs and systemic review of RCTs are really the highest levels of evidence. Now, what this does is enshrines the clinical trials and RCTs in particular as the pinnacle of evidence-based approach to medicine. And it's based solely on the capacity to determine causality because that's actually what that hierarchy is based on.

But it actually perpetuates a terrible, terrible myth, which is that the concept that determining causality is the best way to improve outcomes in a clinical situation. And that is absolutely wrong. Because what is very clear from the experience of registries is that the best approach to getting an improvement in clinical outcome, which is what a registry is for, is increasing the use of approaches that are identified as having the best outcome. So you identify what works. You also identify what doesn't work. And if people continue to change from what doesn't work to what works,

you'll get an improvement within the healthcare delivery.

And there's nothing in there that says that you actually have to understand what the causality of the problem is. In fact, I've talked about the ASR prosthesis. Still today we actually don't know why that device fails. There are multiple reasons probably, but, in fact, it doesn't matter. All that needed to happen was a system be in place to identify that it didn't work. And that's actually what happened.

Other approaches to assess the value of a registry rather than its ability to assess causality could be the capacity to provide new information. Well, registries are really up there with respect to doing that.

Applicability and relevancy of the information. Well, registries are up there with the ability to do that because they can actually provide surgeons with their own data and outcomes.

The ability to produce beneficial change. There is no question that if you ask orthopedic surgeons, particularly in countries that do have established registries, whether their outcome has been affected by looking at the results of clinical trials or randomized controlled trials -- I've asked this universally at many orthopedic meetings, and no one puts up their hand and says that has happened. If you ask them if their outcome has been affected by registry data, which is their own data, they will all universally say yes.

International collaborations are also very important, and with arthroplasty registries there's a very well established system for doing that.

The International Society of Arthroplasty Registries was established in 2004. And so, there is an understanding that linking registry data and registries working together is a very important principle.

And the FDA has been fantastic really in supporting that collaboration with the development of the International Consortium of Orthopedic Registries in 2011. And we will talk more about that later today.

In summary, registries are a continuous, ongoing quality assurance program. The newly established registries are building on a wonderful legacy that was actually established by Scandinavian and the Swedish registries in particular. Worldwide patients, surgeons, hospitals, industry, regulators, and governments are increasingly embracing the use of registry data. Registries are relevant, useful, and they do make a very big difference. Expanding the role of registries can only be to the benefit of patients. International collaboration will further enhance registry effectiveness. Thank you very much.

(Applause.)

DR. DANIEL: Thank you, Stephen. Our next speaker on the agenda is Trish Groves. Is she on the phone? Okay.

Trish, are you on the line and can you hear us?

Okay. Should we go to the next speaker perhaps and then --

She's going to call now?

DR. MARINAC-DABIC: Trish Groves is the editor from the *British*

Medical Journal. And I just wanted to say a couple of words about her support throughout the process.

(Phone rings.)

DR. DANIEL: Okay. Trish, are you on the line and can you hear us? Trish, are you there? Trish, are you on the line?

DR. MARINAC-DABIC: I just wanted to say that we've interacted with Trish Groves as part of this building infrastructure through Cornell University and convening the IDEAL meeting of the IDEAL initiative where Trish was an integral part of and very, very supportive throughout these couple of years. She wanted to be here in person.

As many of you know, this meeting originally should have taken place in April and then May and June and we got moved to September. And, finally, something else intervened, and she had to be on another location. But we were hoping that we are going to be able to hear her presentation because the support and the understanding from major medical journals are so important to the success of this effort. And we're happy to have Bill Summerskill from *Lancet* here today, and Trish, I hope, is going to be able to join us via phone.

We also invited *New England Journal of Medicine*. Unfortunately there was another scheduling conflict, but we'll continue engaging the community of the scientific publishers to help us spread the message about this effort and to help us multiply interested parties in various

clinical fields.

DR. DANIEL: Trish, are you on the line? Hello, Trish, are you on the line?

DR. GROVES: I am. Hello.

DR. DANIEL: Oh, great.

DR. MARINAC-DABIC: That's great.

DR. DANIEL: Good morning.

DR. MARINAC-DABIC: That's -- applause.

DR. DANIEL: Okay. We have your slides queued up.

DR. GROVES: Oh great --

DR. DANIEL: So feel free to start -- excellent. Thank you.

DR. GROVES: Great. Can you hear me okay?

DR. DANIEL: Yes, we can.

DR. GROVES: Good. Okay. Actually, I won't need my slides -- I've seen all the others -- but -- oh, there they are -- all right, let's go. So you're ready? I'll go?

DR. DANIEL: All set.

DR. GROVES: Okay. Good. Well, I'm allowed to speak for 5 minutes, so I'll try and stick to that. And I'd like to talk a little bit about background, about what works now and about what -- there are and then short-term and long-term priorities. I'll try and run through that pretty quickly. Next slide, please.

Okay. Can you see it? I haven't got the next slide up yet --

DR. DANIEL: Yeah, I think it might be delayed, so we do have the next slide up.

DR. GROVES: It's -- from a paper in *New England Journal* earlier this year by Resnic and Normand. Do you have that slide?

DR. DANIEL: Yes, we do.

DR. GROVES: Great. Okay. I mean really -- be there. You know, this is why we're here. But the point is that the whole story of devices is a moving target. What we're all trying to do is to balance the understandable pressure to get devices to market quickly ultimately to benefit patients. But, we're trying to balance that pressure and that speed against the need for decent -- that devices not only benefit patients because they work but because they're safe, and that's what we're all trying to do.

Now, I'm speaking here as a journal editor. A journal is read by doctors, and it's read by policymakers. It's an international journal. And, I have a conflict of interest in that my journal, the *British Medical Journal*, the *BMJ,* has been very critical to date of the way that devices do get to market. And, we have published research, original research, we've published investigative journalism, and we've worked with the BBC and other documentary TV companies here in the U.K. to make documentaries in the past year or so about the problems with some devices, particularly those metal-on-metal resurfacing devices for hips. But, generally our -- journal is

pretty skeptical.

Having said that, we also have published and are publishing studies based on registry data, and clearly everyone agrees that there is much good to be had from registries. But that's the background, and that's where I'm coming from.

The next slide -- I think probably there's nothing on this slide that you haven't already discussed. I mean you've already heard about INTERMACS. I don't know if you've heard about SWEDEHEART, but, again, it's a device registry that's been going for quite a while, and it's very complete and very useful indeed. We'll have the next slide --

This one is a screenshot of the U.K. National Joint Registry. Are you on the same page as me?

DR. DANIEL: Yes.

DR. GROVES: Yes? Okay. Good. Now, again, this may look familiar to you, but there are lots of different registries. But, what's nice about this one from the point of view -- my point of view as a journal editor in terms of -- very prominent link on the home page to research. And, if you click on that, it takes you to published studies. It gives very clear advice on how to contact the registry because you're in independent research and wanting to do a study. There's lots of information there for the public about specific data, the annual reports. It's all very clear and transparent. In fact, it's pretty admirable stuff, and it's certainly -- interested in transparency and

making research as easy as possible --

Now, we heard earlier -- actually, that's all very well, but there are real problems with who's got access to the data in registries and their governance. And, I would completely echo the need for extremely clear research questions based on pre-specified analyses. Because what we all want to know in the end, that what -- the studies that get published actually are true, they're scientifically sound, they're not biased by commercial considerations or anything else, and you can trust the results. They're meaningful. Because that's what in the end surgeons and physicians who have to use devices and the patients who end up getting the devices put into them or using them to match their conditions because that's what we're all trying to get.

Okay. My next slide. Before, everyone's made the point that there are lots of different registries, and I had a look at the American Joint Replacement Registry, which is pretty new, so I hope you've got a map of the U.S.A. there. It isn't about who's voting what, although -- anyway I won't comment on politics. That would be a very bad idea. This is not about what people are going to vote.

This is about which states are currently participating in the American Joint Replacement Registry and which ones are in the process of enrolling, so there's real opportunity there, but there's still some way to go. And you heard earlier from Michael Mack who was telling us about the STS

national database. And, again, it sounds like it's going to be great, but it's still got a way to go. Next slide.

This is familiar probably to many of you in the room because this great report came out on Friday from the FDA CDRH, and that picture, that figure kind of sums up a lot of good stuff. And, sure enough, registries are there very prominently at the bottom of that picture. I haven't got time to go into all the opportunities that this presents, but I must say it's a pretty impressive and encouraging document, and I'm very glad to say that the *BMJ* has already publicized it. We had a news story published about it yesterday. It's up on our website already. Next slide.

I'm nearly there. The next slide is the highest priorities, and this is over the next three years. Well, obviously we all agree that -- I hope you've got that slide, yeah? We all agree that we need more registries. But, it isn't just the data. We need the methodologies so that we know what to do with the data. And, I hope that you've already heard and will be hearing more about MDEpiNet. I haven't got time to tell you more about that.

Buried in the MDEpiNet report and all the information online about MDEpiNet is something about the collaboration called IDEAL, which is about trying to develop really good study designs for making sure that surgical innovation goes as smoothly as possible and is -- manages to balance what patients need, what companies need, and what we all need in terms of public health. And, my next slide says a little bit more about this, but you

have Bill Summerskill from *The Lancet* in a later session, and he will be telling you more about IDEAL.

There's a very high priority in the next three years, I would argue, is independent research using registry data and really good setup for independent researchers to come with a good protocol for a study and to have the peer review. And, again, Michael Mack was telling us a little bit about how that works in the registry that he's involved with, and that's very good.

Again, as a journal editor, what I'm interested in is not just scientific transparency. You've got a good research question, you've got a pre-specified analysis, you've got a peer reviewed protocol, but you also know where the research question came from, who the investigators are, who's got an interest in this study, who's got a stake in it. So it's very important that conflicts of interest, whether they're clinical, academic, or commercial, are properly declared in published articles about registry data. Last slide -- pretty much my last slide.

This is slightly longer-term priorities, and you've heard a lot about the need for linkage. It's all very well having lots of registries. That's fantastic, but what happens when you have lots of different registries in different countries with different datasets, plus you've got the premarketing studies and you've got surveillance systems and all the fat, and someone smart is going to have to try and link all this stuff up. That's probably going to

take longer than five years, but I hope that certainly by five years time out from here, there will be good examples of very effective linkage.

And then, just again a brief mention of this IDEAL collaboration. This has been outlined in a series of three articles in *The Lancet* back in 2009, but there's another series of articles coming out soon on this. This is an international collaboration, as I've said, on trying to really rethink the way that surgical innovation happens. In the past, surgical research has too often involved people saying, okay, I've done some cases, this is what we did, I've written it up, and now that means that this operation, this device, this technique works. Well, that is very limited type of evidence.

And, the IDEAL collaboration is working on ways to have a sort of iterative approach to research so that at each step of innovation you have different ways of sharing the information, sharing the expertise, and really understanding what works and what doesn't in terms of new surgical techniques and the way surgical techniques interact with the insertion of devices.

So, that's my lot, and thank you very much. I'm sorry I couldn't be there in person, but I was very glad to be able to join you at least by phone, and I've been listening in for an hour, so it's been very interesting. Thank you.

DR. DANIEL: Hello? Thank you, Trish. Thank you very much for that great presentation.

Our next speaker is Anna McCollister-Slipp.

MS. McCOLLISTER-SLIPP: While they're pulling up my slides, I'd like to start with a couple of comments and a disclaimer, and I'll try to keep my slides and other comments very brief.

One is, as a patient I'm very encouraged by the fact that there are this many smart and dedicated people who could come together on such short notice to make this happen. And, I think it's incredibly impressive that Danica and Ben and others at FDA were able to pull this off.

Secondly, a couple of disclaimers. I'm not a physician. I'm not a researcher, although much to the disappointment of my husband and close friends I tend to play one sometimes at cocktail parties. I'm not the expert in the room in terms of creating registries and structures. I sort of play with data a little bit because I'm sort of a nerd, but I'm not here to tell you how to create a registry. I'm here to give you a perspective of patients on what this means for them and what we want out of something like this.

And, then my third and final comment and disclaimer is that as you've probably figured out over the past couple of days, I'm not your typical patient. And, again, my mother would -- an endocrinologist -- would probably agree that's probably a really good thing for society, but -- first of all, I have Type 1 diabetes. That's very different than some of the disease conditions that are represented in the registries we've been discussing. I don't have any cardiac implants. I don't have any joint replacement procedures. I hope to

keep it that way.

But the type of devices that I have are ones that I interact with on a regular basis that, again, as I referenced the other day, kind of bridge medical device and consumer electronics, so I want to preface it with that. Secondly, I don't pretend to represent other people with other diseases and other concerns. I think often when you come to these policy conferences, patients are referenced as some sort of like weird, amorphous monolith of opinion. There are a lot of people who have lots of different opinions.

I'm comfortable enough with my disease, with the fact that I have complications. I'm motivated enough and again sort of nerdy enough to be able to come here and talk about it in open. That's not the case with everybody. Sometimes this is very sensitive. Sometimes it's scary. So, again, take my comments and remarks within that context, and I'll try to be succinct.

As I was getting ready for this, I did a little bit of research, and I didn't have all that much warning like the rest of you, but I sent out some quick e-mails and did some quick surveys through some social networking groups with Type 1 patients. But I also -- because I know Type 1 patients can be a little bit different, I also talked to people who don't have Type 1 diabetes, who have -- are sort of 40-something, middle-aged, older, to get their thoughts on some of these things.

And, the biggest comment after they realized I was going to force them to talk about something that would probably bore them was, wait,

what's a registry? And, it's often followed by things like you mean like the Nazis do or did? Are people going to keep a list of all the folks who have diseases? One person asked me if this meant that FDA was going to give them gifts from Pottery Barn and Neiman Marcus, a/k/a a bridal registry.

And, I talked about this some yesterday. We don't -- patients as a whole don't think about things in terms of registries. It's jargon. It happens in every specialty, it happens in every professional world, but registry is not something that means anything to anybody within the context that we're discussing it.

And, then after you kind of tell them what it is, they say, but don't they already do that? And, one thing that I'm constantly surprised of is people assume that we're better than we are. I can't tell you how many physicians I've gone to and specialists that think that I have a continuous glucose monitor and a pump, so therefore this continuous glucose monitor doses the pump and controls my diabetes and keeps everything in perfect check. That couldn't be further from the truth. There are a lot of people who are investing in that kind of stuff, some JDRF and lots of companies like Medtronic and others are really investing in making that happen, but we're a long way away.

I'm always kind of stunned with the fact that people are surprised that their doctor doesn't have access to their electronic medical record that they gave to the emergency room two days ago. To some extent

people think that we're doing some of this stuff. And, then when you talk a little bit further and they start to really get their head around what it is and you start using words like surveillance, monitoring, postmarket studies, they come up with, surveillance? Are people going to be able to Google my health data? Is this what NSA does? Are they going to be listening into my conversations? How am I going to be penalized, and what is this data going to that could potentially harm me?

These are very real concerns. And, as we think about how we move forward, how we put together the -- with the steering committee and how we put together the structure for this, we really need to think about how do we get by in not just the medical and research and regulatory and political communities, but what does that mean from a patient perspective? And, how do we talk about these in ways that actually make sense in the lives of patients who ultimately just want to be healthy, want to be safe, they want to live their lives without having to worry about this stuff.

Just very briefly, I'll talk a little bit about what I think we want. And, again, this is based on a very unscientific, very biased sample of people who are involved enough in their disease to be on diabetes chat rooms or social groups or to know me as a personal friend.

Security is a huge issue, and it's security in different ways. I mean people -- again, unlike me, a lot of people don't want others to know that they're sick. They want to be in control of that data. And, even if they

do tell people about it, they want to be able to determine who knows that information and what are they going to do with it.

Some people are concerned about their personal information. My husband actually was a victim of identity theft a few years ago that happened because he switched doctors and somebody was stealing medical charts from the doctor's office. There was a big ring that was investigated, and fortunately they stopped it, but that's a real issue too. And, that's something that people think about. When we go to the doctor, we enter our Social Security number, our insurance ID, I mean sensitive information in terms -- it's not just about what is my disease, but what are the other things that people can find out about me that I don't want in the public domain.

What are researchers going to be able to see about me? And I tried to assure them for the most part researchers don't really care that much about who you are and what you're doing as an individual patient. They're looking at large global outcomes, and they're trying to make decisions based on large population studies. And, that helps, but it's funny -- and this is probably a D.C. bias, but most people say, well, I get that, but the other people aren't going to get it. You can't talk to the people in places like Ohio where I grew up and expect them to understand this, but I'm smarter than they are because I live in DC and think about things like this so I'll be able to get it. Whether or not that's true, I don't know, but it's a typical DC attitude.

And then, finally, we're constantly hearing about security

breaches, not just within the medical field, where somebody takes a laptop and leaves it in their car and it gets stolen and you have suddenly data breaches of electronic medical records or other types of data, but also groups like the "hacktivists" like Anonymous. What happens if they decide that what FDA is doing or industry is doing is not a good thing? What if they don't trust the process? They've hacked into people who have security companies.

I mean these are creative smart people with a bit more time on their hands than I would imagine, but they're very talented, insightful, and they have a perspective. And, if we happen to be on the other end of that perspective, then there could be some issues that could cause significant problems.

Secondly -- and again, I feel like I'm not being all that brief, but I'm trying to talk really fast – transparency, I think, is critical. What are you going to do with this data? Who's accessing it? We want to know in advance. I don't know how many HIPAA papers I've signed without reading. And, again, I sort of know what's in it. I don't know how many informed consent things I've signed without really getting into it because I want to get in to see the doctor and I still have to list the 14 different medications that I have and fill out a medical history because the doctor can't access that.

What are you going to do with that information? People don't read informed consent. They don't -- and they don't really think about it when they do. They're focused on other things. So, we need to find a way to

be creatively transparent in a way that it will register with patients and will sort of make it through their skull and their thought process as they think about the rest of their life and what this data means.

And, ultimately, especially within the diabetes community, a lot of us are really eager. We generate all this data all the time, and nothing generally happens with it except for our own decisions. People are interested in helping other patients. They're interested in making sure that the data is used for good resources, but they're a little skeptical. Once it's out of their control, they don't have any control of it, and who knows what's going to happen with it. But they want assurances that the data is going to be used for the right purposes.

And speaking of insurance, we need to think about from the patient perspective: Who's going to be looking out for my interests? And, as an admitted comparative effectiveness geek -- I became one because I spent some time living in the U.K. and was appalled at some of the things that I had to deal with as a Type 1 diabetes patient who had no complications. And, again, I know that it's been about 11 years since I lived there, and there have been lots of changes in NHS and there's some wonderful things and wonderful people who are working.

I'm not trying to be critical of NHS, but there are some unintended consequences of things like comparative effectiveness research that we generally don't think about necessarily. Is this going to be used for

reimbursement? I think we'd be naïve to think that it wasn't and shortsighted to think that it wouldn't be insightful, but what does that mean? And who decides what are the critical things that we're measuring within a registry, within a study, in terms of what outcomes are relevant to patients?

I'm on a medication called Symlin. Symlin doesn't have that much of an impact on hemoglobin A1C. A lot of physicians don't use it because there are all these sort of black box warning signals, but there are a variety of benefits to this drug that generally aren't measured. And, I can tell you -- I can get into more specifics about that later for those of you who are interested, but there are unintended consequences that can be very good that affect quality of life, that affect the ability to be compliant or adherent to our regimens, and then ultimately will protect long-term health and keep us healthy over the long term.

And then, finally -- and this is the last one -- we want access. Again, people like me with Type 1 diabetes, we live with data. We see our own data. We are forced to understand it. And everybody I e-mailed and talked to and heard from, based on some of the messages that I put out there, everybody said I want access to the data directly. I want to see how I compare to other people. I want to see what you're doing with all the stuff that you're collecting. And not from the paranoia perspective in this particular instance, but I need to control my disease.

And as I mentioned yesterday, I see my endocrinologist four

times a year. That's four times a year. I have to live with my disease and manage my medication and devices and make decisions on a minute-by-minute, hour-by-hour, day-by-day basis. My physicians don't need that. And, surprisingly, if you look at some of the platforms that are developed for downloading data from devices, they're completely designed to work with physicians and to e-mail that data to physicians.

The way the whole platform is -- first of all, they look like they were built in Windows 95. And it's baffling to me that that's what we have to work with, but people expect it to be like an iPad, like the things like they get on iTunes. They want it to work easily. And, anyway, I mean we need to think about not just how do we use this data that we're collecting? How do we take this effort to inform public health decisions, reimbursement decisions, surveillance monitoring, all of that stuff, but how do we use this to give patients the information and the power and the motivation and the tools that they need to manage their own disease, especially those of us with chronic illness?

This is absolutely critical, and I think it's not just critical to the patients and the lives of the patients, but the more useable and the more accessible you make this to patients, the more comfortable people are going to be in supporting it and letting this happen and go through -- continue over the long haul. Thank you very much.

(Applause.)

DR. DANIEL: Okay. Thank you, Anna.

I am getting in trouble for having this go on long, but we have one more presentation from Jay, and then I think it would be important to be allow some time for questions. With all of these panelists, I'm sure there are questions in the audience as well as from the other panelists as well.

MR. CROWLEY: All right. Then I will be extremely brief. How's that? A number of speakers have talked about Unique Device Identification, UDI. Hopefully all of you are familiar with this. This is a project that we've been working on for many years.

The proposed regulation implementing UDI published July 10th of this year, and I'll put up a website here in a moment where you can go take a look at it. Again, it's something that we envision is going to help us in a lot of the postmarket surveillance activities. It's highlighted in the report. Danica talked about it. And so we do think it's a foundational element in terms of registries. So I'm going to go very quickly into what UDI is. If anyone has any questions about it, please feel free to follow up with me later.

Why are we doing UDI? Well, because as hopefully you all are aware, there isn't a current standardized way of identifying devices. We have manufacturers using catalogue numbers that are the same. And then downstream of the manufacturers, we have all the other stakeholders having to create their own identification systems. Distributors, hospitals, payers, everyone else creates their own way of identifying a device. We do not have

a single standardized way to do that.

Here is an example of that. This is a very simple example. I could provide many, many more, but this is a BD product, and you can see all of the various different identifiers that distributors, hospitals, payers, others use to identify that one single product. This actually goes on for four pages, but I just put up one page of it, and you can see the problem we're trying to solve.

UDI is attempting to create a standardized, unambiguous identification system for all medical devices, which importantly is globally harmonized. We've been working on this, as I mentioned yesterday, for a number of years and are making great strides in that effect.

Mandated originally in FDAAA in '07 and some amendments in FDASIA, which was signed into law in July of this year as well, the non-italicized text is the original legislation, the italicized text is the FDASIA requirements. Basically, go forth and build a UDI system, which is what we've been working on.

UDI applies to nearly all medical devices. Please take a look at the proposed rule for how this plays out. It's applied to basically the unit of use of the individual device, and then UDIs are applied to higher levels of packaging as well: UDIs both human readable and encoded in some form of AIDC linear barcode, two-dimensional barcode, RFID, et cetera. We do not plan to identify any particular technology.

We also have potentially direct part marking for certain types of devices. This is where you put the UDI on the device itself for certain implants, reasonable surgical instruments, other kinds of devices as well. An example -- and hopefully you can all see this. Thank you to our friends from Medtronic. This linear barcode -- hopefully we all know what a linear barcode is -- here in the bottom middle of this label contains what we would consider to be a UDI compliant identifier.

Importantly, it contains two pieces of information. There's a parenthetical one, for those who can see that I hope, and the 14 digits that follows that is the device identifier. And if you were to look up those 14 digits, you would find it's one of these products. Following that is a parenthetical 17 and a parenthetical 10 application identifiers that tell you the lot number and expiration date of this product.

So unlike, for example, the pharmaceutical barcode rule which encodes an NDC number in a linear barcode, the UDI includes not just the device identifier, which tells you what the product is, but it also includes what we call production identifiers: lot numbers, serial numbers, expiration dates. So we're including that information as well so that we can capture this information, for example, in registries. If this had been a serialized product, it would contain a serial number in the UDI. It's a lot controlled product, so there's a lot number. So however that product is currently controlled, whatever you find on the label is what becomes part of the UDI.

One example of what it looks like, here's another example: two linear barcodes in the bottom left-hand corner. Again, the top barcode contains what we call the device identifier. If you were to look up this information, you'd find it's one of these products. The bottom barcode contains the lot number and expiration date of this product, again, because it has a lot number and expiration date. Again, if it was a serialized product, it would have a serial number. Two perfectly reasonable interpretations of what we believe UDI will look like moving forward.

I mentioned before if you were to look up the information, you would find it's one of these products. We are building what we call the global UDI database, which will contain for each device identifier. The UDI database does not contain production identifiers, so we are not collecting serial numbers and lot numbers. It's simply a reference database for information about the device.

For each device identifier, this is the kind of information that we expect will be in the database. This is the list that was published in the proposed rule. We do expect comments on this. And so, if people think there's other information that should be in there, please feel free to let us know. Before I go on -- all of the data will be submitted to the UDI database by the manufacturer of the product, but we do intend to make nearly all of this information publicly available to support the kinds of postmarket surveillance activities that we've been talking about for the last couple of

days.

Implementation is based on premarket risk class with Class III products going first one year after publication of final rule. Danica mentioned earlier that we do expect to publish the final rule May of next year, May of 2013, so Class III devices would need to meet all the requirements of UDI by May of 2014.

One of the changes of FDASIA is this new implementation timeframe for implants and life supporting and life sustaining devices two years after publication of the final rule, the rest of Class II devices three years, and Class I five years after publication of the final rule.

For those who have been marking their devices with NDC or NCDR numbers, important to note that we are phasing out the use of that system as UDI comes online.

We do encourage everyone, device manufacturers, clinicians, others, to submit comments. The last slide will have our web address. You can go there to link to the *Federal Register* notice. Comments are due by November 7th of this year. And, again, we have six months to publish the final rule.

This is the website you can go to look up everything UDI and link to the *Federal Register* notice. And, again, if you have any questions on UDI, please feel free to contact me. I hope I went quickly enough. Thank you.

(Applause.)

DR. DANIEL: Great. Thanks, Jay. I think we'll take questions from the audience as well as if any questions came in from the web. But to kick that off, I do have a couple questions for panelists.

One thing we heard that's common among registries is the burden of collecting additional data elements. And we also heard from Danica this morning that part of MDEpiNet strategy is to maximize the use of EHR data and claims data in device surveillance. So my question to the panel is that we did hear from Elizabeth that Kaiser is demonstrating value in using claims or at least administrative data, for example, pharmacy data, which might help better characterize patients, utilization data. We heard from Michael that the TVT Registry will soon use CMS claims data for long-term outcomes.

My question is why haven't we seen much more maximal use of claims data and EHR data in this registries, specifically on the claims side? Is it a technical barrier to bring in claims to the registries? Is it a motivational barrier for commercial payers and hospital systems and developers of these registries to actually come together and collaborate? So either Rick or Elizabeth or Nancy?

DR. DREYER: I'll offer that there's a huge technology barrier. We ought to start there. There are access barriers, but technology barriers, it's just as simple as you would think.

MS. PAXTON: Claims data wasn't initially developed for registry

use and for assessing clinical outcomes, so it's very limited in doing so. There's also limitations in terms of the accuracy, the sensitivity, and specificity. Within our system fortunately, we have access to our electronic health records so we can identify potential complications using electronic screening algorithms using both diagnostic codes and procedure codes. And we can cast a wide net and then do a chart review looking at the chart to confirm that those cases actually are associated with those outcomes.

DR. KUNTZ: I mean this whole last few days has been about the fact that the data we need is not available. And we wouldn't be building a registry if we could get this easily.

DR. DANIEL: So I guess to add onto that, so we heard that claims data are not valuable for the actual clinical endpoints, but are they valuable for providing a better characterization of the patient? Understanding maybe history from the claims data or what's happening in the outpatient setting, maybe perhaps not a clinical endpoint at this time, but measurement of some common conditions or utilization happening in the outpatient setting that might help at least control for compounding, is there a value in that?

MS. PAXTON: I think there's more value in terms of using that to characterize the patients in terms of their demographics and definitely more limited in terms of the endpoint and the outcome. But that also differs by which diagnostic codes you're using and procedure codes. Some are more

accurate than others.

DR. DREYER: Let me also just add one thing about what you're hearing as a perspective of an integrated delivery network. And for those of us who don't have the luxury of that type of data, claims are useful because they'll tell you prescriptions fills, they'll tell you some crude but useful information recognizing that the average duration of membership in the United States in a health system is two and a half years.

DR. MACK: I think the other use of claims data is to evaluate major outcomes, so for instance mortality, stroke, repeat rehospitalization for specific reasons. Now, one of the problems that's linking them is you can't direct link them because of patient confidentiality issues, so you have to use probabilistic matching. And you can only link about 80% of patients' records by doing that. Once you do link them, the chance that they are linked correctly is very, very high. I understand 98 or 99%, but you're still only able to link about 80%.

The other issue regarding electronic health records is it's not like there's one electronic health record out there. You almost have to pick a partner and go with that one be ever who that partner is because it isn't one agnostic generic system that you say you're going to partner with an electronic health record and now you're speaking to all of them. It doesn't work that way.

DR. DANIEL: Great. Thank you.

We have a question from the audience. Can you introduce yourself please?

DR. TAVRIS: I'm Dale Tavris. I'm in the Division of Epidemiology in CDRH at FDA, and I just have a comment. I'd like to express my disagreement with the idea that registry data does not contribute to an understanding of causality. It does contribute to an understanding of causality because it looks at the relationship between disease outcomes and other factors under real world circumstances. And that's something that clinical trials do not do.

And it's true that unmeasured confounding variables present a barrier to an understanding of causality in observational studies. However, that barrier is not absolute. And, in fact, there are criteria that have been developed to assess the contribution of observational studies to an understanding of causality.

And I'll just end this comment by mentioning the clearest example of that, and that's the relationship between smoking and lung cancer. It's widely accepted today that cigarette smoking is causally related to lung cancer. And that's based almost totally on observational studies because clinical trials would be considered unethical to look at that subject. Thank you.

DR. DANIEL: Stephen?

DR. GRAVES: Yeah, thanks very much for the comment in there

because it can help me clarify a little bit about what I was saying because clearly you misunderstood what I was saying in that I wasn't saying that registries couldn't be used to establish causality. I said that that's actually not what their purpose is.

You're absolutely right in that they can be used to establish causality in certain situations. And the example you gave was smoking and lung cancer. And what a registry could do is, if there was a registry, is sort of looking at smoking and lung cancer and saying if you smoked a lot, you're more likely to get lung cancer. That is an association that it's identifying because there are other factors that may come into the causality. And that's where a clinical trial becomes very important because you're controlling for a lot of factors.

But the point I was actually trying to make was not that the registries can't be used to establish causality, because I agree with you that they can on many occasions. I was trying to emphasize that one of the problems for registries is that people criticize the level of data that is collected in a registry, and saying because it's not an RCT or that it isn't really a high level clinical trial, that it's of lesser value.

And I guess what I was pointing out that the purpose of a registry was not so much to establish causality but to identify difference. And once that difference is identified, then a lot of extra work from a registry perspective goes on to see if there can be reasons worked out why that

difference exists. But the essential thing that we do is that we actually look for difference. And once we have difference, then we can hone down. But it's an entirely different approach to what would be done with a clinical trial. And I guess I was trying to make that distinction.

Thank you for your comments, and I think that hopefully I've clarified that a bit better.

DR. DANIEL: Okay. Thank you. Just one more question? Is that okay? Any questions on the web? Who do I look at for that? Okay. I think perhaps to Anna as well as Nancy, so Nancy you talked about governance and the importance of that. Anna you talked about the needs of patients and having access to data and being able to, I guess, have more innovation in how patients can be involved.

So my question is, knowing that patients come from all different levels of understanding about their own condition, what's the best way to maximize the input of say a patient perspective on a governance or on a steering committee?

DR. DREYER: My experience with steering committees that include patient representatives, they help drive the focus on the outcomes that are important to patients and the questions that are important to them. We heard a great example of the kind of decision making that needs to be made every day during the day, and that kind of focus is just what these kinds of endeavors need. And not just the patients, but the practicing physicians.

The non-academic docs, what do they need?

MS. McCOLLISTER-SLIPP: I don't know if I have the be-all-to-end-all answer to your question. I think there are probably a lot of different ways that you could do it. But I think as a patient who understands both the benefits and potential risks of comparative effectiveness research for my own health and my own ability to choose what works best for me with my position, I think you need to be incredibly transparent, and I think you need to go out of your way to make sure that somebody who can represent the perspective of a patient is involved in every part of the process.

Not just about how do we set up, but how do we ensure this happens over the long haul? And how do you maintain the integrity? How do you keep the objectives of the registry from changing over time? If you're asking people -- actually, most patients don't have a choice of whether or not their data is included in these things. I mean I feel like there's a responsibility to make sure that every aspect, every decision, every consideration is given to include the interests of patients, not just informed and active patients like me, but those who may be less informed and less involved and more focused on other things.

DR. DANIEL: Okay. Great. I'd like to thank all of our panelists, and Trish, thank you for dialing in.

(Applause.)

DR. MITCHELL: Good morning. Let's go ahead and start our

second session. If everyone could please take their seats?

My name is Diane Mitchell, and I'm the Assistant Director for Science at CDRH. I am very, very appreciative to have this opportunity to participate in this four-day event. I think it's really important for our Center to better be able to understand our devices in postmarket.

Our session this time is Using Registries for the Total Product Life Cycle Appraisal of Medical Devices. And just as with the first session, we have a series of invited guests who will be speaking briefly to this topic, and then we will go into a bit of discussion. With no further ado, what I would like do -- actually, two things.

The first one is, sitting in the audience it was hard for me to hear the guest speakers last time. So if you could just move your mikes a little closer, I think that will be terrific. The second thing is that I think the first thing we can do just like in the last session is everybody go around and introduce themselves, and then we'll come back and go in the order in the agenda for the speakers. Does that work for you all? Yes? Good. Okay. All right, so if we can start to my left?

DR. KRUCOFF: Good morning. My name is Mitch Krucoff. I'm an interventional cardiologist and Professor of Medicine at Duke University and the Director of the Cardiovascular Devices Unit at the Duke Clinical Research Institute. And I just want to again, like so many, thank Danica for putting together something quite unique and amazing this week.

DR. ZUCKERMAN: Good morning. My name is Bram Zuckerman. I'm Director, FDA Division of Cardiovascular Devices Premarket.

DR. BRENNAN: Good morning. I'm Matt Brennan. I'm an assistant professor at Duke, an interventional cardiologist and epidemiologist by training, and work in outcome surveillance and large clinical registries with claims data.

DR. STEINBUCH: Good morning. My name is Michael Steinbuch, and I'm with Johnson & Johnson Medical Devices and Diagnostics Division and part of the Safety and Surveillance Center of Excellence.

MS. KUHNE: Good morning. I'm JoAnn Kuhne. I'm here as an industry representative, and I'm the Vice President of Regulatory and Quality for a company called Sientra.

DR. BARBER: Good morning. I'm Matt Barber. I'm the President of the American Urogynecologic Society. I'm a professor of OB/GYN at the Cleveland Clinic.

DR. PUSIC: Good morning. I'm Andrea Pusic. I'm a plastic and reconstructive surgeon at Memorial Sloan-Kettering Cancer Center, and I'm representing the American Society of Plastic Surgeons.

MS. BROCK: Good morning. I'm Janet Brock, and I'm a director in the Division of Operations and Information Management in the Coverage and Analysis Group at CMS.

DR. FRANKLIN: Good morning. I'm Pat Franklin. I'm Professor of Orthopedics and Epidemiology at the University of Massachusetts Medical School, and I'm here representing the AHRQ-sponsored function and outcomes research collaborative for total joint replacement evaluation.

DR. IGLESIA: And I'm Cheryl Iglesia. I'm an Associate Professor in OB/GYN and Urology at Georgetown, and I'm representing ACOG and also as the guidelines committee for the Urogyn Society, AUGS. Thank you so much.

DR. MITCHELL: Terrific. And now if we can get started with the presentations, we could start with you, Mitch.

DR. KRUCOFF: Well, the good news is some of my work has been done because some of the things I'm going to mention were discussed in the previous session. And then, as we are a mixture of new and old attendees relative to yesterday and the day before, a couple of slides I'm going to show are slides we showed earlier in the week, but I'll try and be focused.

The key I think first is to understand this is a set of slides that David Feigal actually sent me when he was the Center director as the concept of the total product life cycle emerged. Within the total product life cycle, I think we recognize there are a lot of processes involved at different stages of the lifecycle of a given device. And within those there are a number of places where human clinical research data or outcomes data are applicable at least

to, I think, our understanding of a device.

Importantly, though, I think we have to recognize that different devices have different degrees of maturity as well. So when a first breakthrough device like the CYPHER drug-eluting stent is a first-in kind, that actually was highly informative then to our understanding of the next breakthrough or the next iteration, if you will, in a competitive device space.

And, in fact, the development of those competitive variations on a device create a pipeline that in drug-eluting stents in the United States would look something like this at this point in different stages of evolution. But this is a mature pipeline as opposed to starting with a TAVR where we are really in the breakthrough first phase. And along a pipeline from breakthrough to the 14th iteration, we also change our needs for what types of processes or even what types of clinical trial designs, active control versus placebo control, et cetera.

So I think as we move forward in this discussion, we have to recognize the depending on not only where an individual device is in its total product life cycle, but the maturity of the pipeline overall will also vary the degree to which registry data may or may not be applicable.

This is a slide from yesterday, and this to me is what's our problem is that traditionally where finances were generous, everybody could do their own thing their own way and find a way to pay for it and everybody had their own agenda.

And that has left us in a time of economic constraint with research and development pathways that are slow to the bedside, that are expensive, that are unpredictable, that we're not even very good at coordinating the equipoise between how fast is fast enough for a new device, how safe is safe enough, and the balance between those two, and a lot of unknowns from premarket randomized trials into postmarket real practice of medicine: What's going to happen that's not expected? How do we track it? How well do we understand the actual practice of medicine, for instance, to be able to have an informed consent discussion with a patient at the bedside and really be informed about what the risks and the benefits are?

So this was the focus of a paper that it was my privilege to work with past presidents of the American College of Cardiology, Ralph Brindis and David Holmes, and the Society for Thoracic Surgery, Mike Mack, to focus on where we need to in device innovation, and where this room for this week clearly reflects that we are an ecosystem of multiple stakeholders, and at a time of economic constraint where redundancy is killing us, that the best thing we can do is focus on alignment of processes and objectives that eliminate redundancy.

And I'm going to give just a couple of examples of how eliminating redundancy in fact can improve quality, speed decisions, and move us in the kinds of directions that I think is the spirit of the MDEpiNet and today and tomorrow's meetings as well.

Secondly, I want to say that maybe this next slide is the most important slide I think I'm going to be discussing, which is what are we talking about when we're talking about registries? And I can't recreate the patient perspective. I'm now talking about the scientists' perspective where we tend to get lost about whether we're talking about the content of registries so we have longitudinal data, which is non-randomized, which is suitable for a number of very important kinds of retrospective analysis using the data that's there or data that's available. That's one look at a registry.

But very importantly, we have a whole other agenda for use of registries that are active and ongoing, which is as infrastructure, as infrastructure that is already installed, that is operational, that captures data that is already sustainably funded, that has quality controls that has and applies standardized definitions that is a river of electronic information. And as we do prospective randomized trials embedded in that kind of infrastructure, costs are reduced, efficiencies are increased, quality is preserved. These are suitable for serial prospective observations if we have a signal and we want to confirm it prospectively. And these are clearly suitable for IDE type applications throughout the total product life cycle.

So to me this is the most important distinction, first, is are we talking about what do we do with the content of registries or what do we and how can we leverage infrastructure? And infrastructure for somebody like me who works at a place called Duke where site-based research takes months

of internal negotiation as to how to get up and going, infrastructure from an existing registry is the key to a lot of issues that are not regulatory issues at all. They're site-based issues. But for the industry, for the cost and speed of research in the United States, these kinds of preexisting ongoing operational infrastructure issues at the site-based level have enormous impact on our potential to participate in device evaluation.

Okay. So just a couple of quick examples of what do we mean by alignment of objectives, et cetera? One I think is just to get us all speaking the same language. And I'm not talking about whether Americans can actually speak English, which they can't and we know they can't, as Rick illustrated, but actually in the definitions of outcomes. If we have 50 different trials of the same device that all use 50 different definitions, then we know nothing in accumulating, no matter what the statistical method information.

And here I think the Academic Research Consortium at least serves as a good model. It's a group of academic research organizations and the FDA who came together and continue to develop pragmatic consensus definitions specifically for pivotal device trials. Not as a professional society, not as world health organization, but specifically for pivotal device trials. And we have focused and put these definitions in the public domain through peer review publications, on drug-eluting stent endpoints, on aortic valve endpoints, on bleeding endpoints, and have active fairly advanced areas in

atrial fibrillation ablation, in microvalve, in peripheral arterial intervention, and in quality basics for these kinds of trials.

And we align these. With CDISC, NCDR, other professional societies, leveraging is what alignment is about. But this is uniquely focused on pragmatic definitions. And as an example, the AHRQ stent thrombosis definition published by Don Cutlip in 2007 has now been applied in more than 500 published study reports in almost two dozen drug-eluting stent platforms that all use one definition for this rare but catastrophic and critical safety concern endpoint. That is what lets us aggregate real information throughout the total product life cycle and pipeline of drug-eluting stents.

Aligning the clinical and clinical research enterprise. Again, at Duke, traditionally we have nurses who take care of patients, and then we pay a whole separate army of nurses to fill out case report forms to do clinical research. We can't continue to do this.

So two very brief examples of how can we align our clinical data and our clinical research data into a single enterprise? This is the SAFE-PCI for Women study. This is a public health study supported by multiple vendors in industry and the Office of Women's Health and FDA. It's a very basic randomized trial of femoral versus radial access bleeding complications over 30-day outcomes in women undergoing PCI. It is the only study in the United States in interventional cardiology ever dedicated just to women, so I'm very proud of the public health message.

The science is pretty good. It's a randomized trial. But probably pertinent to today, the most important thing about this trial is that the sites participating in this trial are all already in the ACC/NCDR CathPCI Registry. So 100% of their percutaneous interventions and cath procedures are already being entered by the hospital system, not by an army of research nurses, to be captured in the NCDR. Within that 100% cath lab activity are the patients who are randomized in the SAFE-PCI for Women protocol.

So through a very modest grant from the NIH, we created the National Cardiovascular Research Infrastructure, which is really just an electronic bridge that identifies randomized trial patients whose data already are in the NCDR and pulls them over to the NCRI to a Part 11 compliant informed database. We can talk later maybe about the NCDR is a flat database, but an informed database that's suitable for submission of IDEs with audit trails, et cetera.

So with a very simple step and with a very important partnering and willingness by the ACC and the NCDR to allow this to happen, we have a clinical trial environment that reduces the onsite workload of the coordinator 65% per patient. Sixty-five percent of the work is already there through the data entered in the NCDR.

Another piece that we heard extensively from Mike Mack about this morning, but is a very critical proof of concept for aligning, approval, and reimbursement decisions, is the TVT Registry. And Mike explained this is

itself an important alignment between surgeons and the surgical professional society STS and cardiologists and the ACC working together rather than independently with the same objective, now through one process rather than two that would have to be pieced together later.

Using the valve ARC definitions -- now, hopefully, if we have discussion, we can see later there are some devilish details. So the VARC definitions in the TVT Registry, there's already VARC II. They've been modified. So a database, a registry is a living thing. How do you maintain it? How do you update it? How do you maintain legacy analyses versus new analyses? A whole arena for discussion.

But as Michael also mentioned, CMS stepped forward and not only created the coverage determination that means if you want to be paid for putting in your valve now that it's approved in the U.S., you have to put the data in, but also aligned it to the next level of regulatory decision for the next cohort or partner beyond inoperable patients, that if the indication was extended to high-risk surgical patients based on the FDA's determination, that the CMS coverage determination would automatically extend. Not two processes; one linked process: alignment.

Lastly, and I'm going to be very brief here because later today we'll have time for this, but global alignment, we no longer have just a universe where research in the U.S. is good and research everywhere else is not. In fact, in many cases we have excellent research with devices outside

the U.S. that are not even available in the U.S. yet. So how do we preserve international jurisdictions but work together?

And registries certainly as an infrastructure provide one critical and obvious fundamental way that we could really work together. The HBD program we'll hear more about later today, but Japan and the U.S. governmentally through regulatory authorities, participation of industry, all stakeholders, academics, good model.

And then newly formed the International Medical Device Regulators Forum launched just this past February. I don't know if February 29th is an auspicious day or a worrisome one, but anyway, we'll see where this goes. But, again, regulators working directly together in the harmonization and convergence universe. And in case anybody thought we were going to lag on that, the Obama administration has made it clear through an executive order that this is important.

Again, this is the main point, I think, as we talk about registries: what's content, what's infrastructure, and where does it fit in the total product life cycle of novel breakthrough devices out to the most mature device spaces? Thank you.

(Applause.)

DR. ZUCKERMAN: Good morning. Again, Danica had extremely important and well thought out comments to open the meeting this morning where she talked about how we can integrate registries in a stronger

postmarket environment into the whole device approval process. And I'm just going to give some thoughts on that key point in a series of questions by using the FDA Division of Cardiovascular Devices perspective.

And to appreciate where I'm coming from, I just want to take a step back to highlight some key things that are part of our pre-approval device evaluation process. I think many are familiar with the fact that we use a risk-based paradigm so that the level of evidence pre-approval is dependent on the risks posed by the device.

This must not be FDA approved. It doesn't work.

Okay. It's working. It heard me. Okay.

Now, in the cardiovascular device space, we're mainly talking about PMAs where registries have a high degree of utility. And certainly pre-approval requirements are a reasonable assurance of safety and effectiveness. We can see how detailed the requirements are, and we're certainly not talking about changing the bar today. And I think many from the industry and investigator community know that there's a phased approach to medical device development, but at the end of the day, to get a device approved, PMA device in the U.S., one should show clinically significant results as well as safety.

And to do that certainly as talked about in the first session this morning, quality by design for registries, we have analogous metrics for quality by design for pre-approval trials. And that's all fine and good and

there are many sponsors really doing a very laudatory job here with the device approval process.

The problem becomes, however, as noted by Danica and multiple other speakers, including the guy to my right, that we need to regulate devices throughout the total product life cycle because, frankly, device approvals are usually for a reasonably narrow indication. There's a lot of iteration, and to put together a device approval process and just as importantly a device availability process for the American public, we need to work with some tradeoffs. And, consequently, the importance of the postmarket arena and process is highlighted.

I think what is shown on this slide are the usual things that we're looking for post-PMA approval. Certainly we want to make sure with the FDA-approved indications that operator device learning curve, long-term durability, and other rare events don't become an issue. I think we're also looking to demonstrate again generalizability to the U.S. population. However, as noted this morning, though, there are a lot of other good uses for registry, including learning, promoting public health, et cetera. And certainly from the premarket perspective, we want to encourage this.

The devil is in the details, however. For many of these interesting questions, post-approval registries can continue and thrive without an IDE or investigative device exemption. However, as many from the industry will tell you, that when we're looking at new indications for use

for significant risk devices, we do need to do these studies under IDE.

Now, the good news is that certainly in most cases we're talking about already approved devices, so the key points of the IDE are not the pre-clinical safety data. They're the informed consent protocol issues, which are very interesting issues. And one thing that we should talk about in the Q&A is how can the case report forms be designed such that for these adjunctive IDEs, we're not developing new case report forms or definition as Dr. Krucoff just mentioned. But we do want to recommend again that we use our standard procedures pre-IDE meetings to really make this an efficient process.

The other thing that I'd like to talk about is that registries have defined purposes. And certainly in the first session, I think there was a lot of good comment there. But for device knowledge and public health to move forward, I think just as importantly we need to acknowledge the limitations of registries when there are important issues that really can't be answered by registry studies. And certainly my response to Dr. Krucoff would be that when this is the case -- and then we're usually talking about expense of studies -- certainly the three branches of HHS are interested in meeting together with sponsors and investigators to optimize the way important randomized controlled trials can be coordinated. And I've put a few examples on the bottom.

Certainly in the case of the public access defibrillator or the

most important question with drug-eluting stents, what objective antithrombotics should be utilized, I mean I think people recognize that a registry could not answer these vital questions. And certainly I've put a few other areas where we have to acknowledge that all stakeholders need to work together, but a registry may not be the right paradigm. Thank you.

(Applause.)

DR. BRENNAN: Thank you for the opportunity to come talk tonight or this afternoon. Thank you.

The initial topic for discussion was registries for research that I was given. And since the DCR has been in this business for 40+ years, that was somewhat daunting, so I've limited it today to what I think is maybe even a tougher job in some ways but a much more important job. And that is my objective in this talk is to help crystallize an idea that we have been batting around, and that's the idea that registries are a tool.

Registries are a tool for data collection. Registries are not a method. They are not equivalent to observational analyses. Registries are a tool for data collection, just like randomization is a tool for data collection. And hopefully in this talk I can show you and together we can go through examples of how truly the efficiencies that can be built into registries can be used in my view throughout the total product life cycle with the necessary quality data that's needed in each of those applications.

It's not a small task, I understand, but hopefully I can take you

through it. And I apologize for deficiencies. Those are not deficiencies of the method. Those are deficiencies of my communication.

Our current system. Our current system is what I would call a fragmented view, so it's a view that involves a product. The center of industry develops a product and then develops a platform from premarket through postmarket through comparative effectiveness and surveillance down the line centered around a product. And what I would suggest is that that view of the world is broken and has serious deficiencies.

Those deficiencies start with the inability to generalize off in that data. And I could show you slide upon slide upon slide of examples where postmarket studies are not generalizable to or even premarket studies are not generalizable to the overall population being studied.

The second is they give us -- do not allow typically the ability to compare throughout the lifecycle of a product, so back to the definitions that Mitch talked about. Inability to synchronize definitions has meant that we're hampered in our ability to use data from one development phase to the next.

The second is, and this is important I think, especially in today's day and age, that they're inefficient. So the current fragmented view of the world, the current reconstruction of platforms and of infrastructure means that we are constantly chasing our tails having to rebuild infrastructure. And this is horribly inefficient. My hope is to move us to a place where we can start to think about the world not as requiring counseling for industry -- if you

can't see it from the back, the caption is reading, "And if you ever did catch your tail, are you sure it would make you happy?"

And so, I don't want to think of the total product life cycle as a dog chasing its tail, but rather as a unified vision of the world. And that's where I'd like to get us to and I think where we're moving: from a fragmented view through to a unified vision with either a disease or a registry at the procedure at the center of that rather than a product at the center of that. And I think that's the crucial message here.

The vision itself. The vision is based on the idea that at the point of care, a lot of data is collected. Whether that's in EHRs or in registries, that data is collected, and we ought to take advantage of that information. We can randomize at the point of care. We can randomize using that information that's collected. We can then use both a registry and administrative data to efficiently follow patients with high quality data through time. And there are innovations to TVTR, which we'll talk about in a second, implements, innovations, and efficient algorithmic adjudication of the endpoints for important safety endpoints that I think could meet most of our bars for what is high quality data. This is the vision for a platform that can move us from a fragmented view to a unified vision.

Examples of where this can be applied from the premarket IDE to post-approval studies; I'll give you examples here of label extension, real world comparative effectiveness research that we've done in automated

safety surveillance, all of this built on the same infrastructure, importantly all of it built with efficiency. Efficiency through innovation is what we're shooting for here.

Registries for premarket IDEs. The traditional approach is registries being used for study planning, for investigator identification, for potentially patient identification, and then it stops.

Why not build a system like Mitch has built and collaborators at the ACC, with the NCRI, with NIH? To randomize off the registries to take advantage of that information, why not use mechanisms that are in place to efficiently track what I consider important clinical outcomes, the outcomes that matter to patients. Patients don't care if they're left with 1+ AI at the end of a TAVR procedure. They care if they've got heart failure. We can follow that in claims data. We can follow that with algorithmic adjudication.

An example of randomization off of a registry, an example of data quality shipping data to the Oracle database, which is a Part 11 compliant database that meets registry -- regulatory requirements, the SAFE-PCI accomplishes this. It's a proof of concept project that shows that registries again are not a method. Registries are a tool for data collection.

Registries in the post-approval studies, potentially label extension, IDE label extension studies. This is an example from the TVT Registry of the design. Information entered at the point of care, clinical follow-up being done out through a year with information by standardized

definitions of endpoints being input directly into the registries and then using Medicare data in these elderly patients to follow them out over time. I think beautiful examples of how a registry can be used for both post-approval studies and label extensions that are in practice now.

Comparative effectiveness research. The question was asked why aren't we using claims data more for research? The answer is we are. We are. Three years ago we came up with the methodology. We have last count at least 15 manuscripts right now that are in publication using this and moving toward another probably dozen that are on the docket. This is coming. This is coming. Use for comparative effectiveness research certainly is there.

We talked yesterday about the use of this data. This is again collaboration both with the societies, the STS and the ACC, and the FDA to come up with what is truly a protocol system for tracking devices over time, a ready prototype to move into the surveillance world using this hybrid model that I talked about.

Is it all sunny fields and blue skies? The answer is no. We still have challenges. The challenge -- some of these we talked about before. How do we capture data -- what I'm going to call data loss? We know that often in the European market, for example, devices are quicker to the patient bedside. How do we capture that information? Through international collaborations. Societies are actively working on that now, and I think these

efforts are underway, so international collaboration.

What do you do about orphan diseases? Either incentivizing the development of further registries around those or use of electronic health records are other ways to get into those fields.

Data quality. I'll say data is not just about auditing. Data quality is also about making sure that our endpoints are validated. And I was excited to learn yesterday that we were funded on a grant from the FDA specifically to look at using claims data and clinical trials data, merging the two to validate these endpoints and make sure that the quality of the endpoints fits what we need in the pipeline and where we are in the pipeline, as Mitch mentioned.

And then, finally, the idea of funding, what is the business model? And I would say that the business model is pretty straightforward. I think this vision is one that through collaboration, we all have a vested interest in making sure that we build innovation into this system, to make sure that we -- for our patients' good, that we move toward a system that's as efficient as we can.

From the regulatory perspective, I think the business case is clear. Reasonable assurance of safety. I believe that following -- using the same mechanism of data collection and registries throughout the total product life cycle allows a greater reasonable assurance of safety from the patient and the provider, and society's perspective gives us earlier access to

technology and better assurance that that technology works when it rolls out to patients. From an industry perspective, importantly, clear business case: earlier to market, limited liability, and design efficiencies that can lead to tremendous -- we've already seen it in the TVTR -- tremendous cost savings while preserving the quality of data that's collected. Independent of perspective, the case for enhanced medical surveillance and the case for using a tool, registries, clinical registries throughout the total product life cycle, in my opinion, is very clear.

Thank you for this opportunity.

(Applause.)

DR. STEINBUCH: I would first like to thank the organizers for the invitation to share an industry perspective on the use of registry data for evidence appraisal throughout the total product life cycle.

This side contains my disclaimer. I am an employee of Johnson & Johnson.

I would like to begin by sharing the AdvaMed perspective on registries. AdvaMed acknowledges that well designed and executed registries can provide very useful information on safety and effectiveness of medical interventions. Sponsorship can vary according to the needs of the stakeholders involved.

A medical device registry can achieve one or more key objectives as listed on the slide, most of which you are probably very familiar

with and most have already been discussed by other speakers this morning, so we'll move on.

The next two slides outline the AdvaMed registry principles. Device innovation is an interim process, and the lifecycle of a product is typically less than two years. Thus, a long-term registry must take into account the potential for next generation devices entering the market during the data collection period. Existing data in ongoing studies should be clearly identified, evaluated, and considered for their depth and rigor compared to a proposed registry. The analysis should also assess whether the estimated timing and cost are merited by the public health benefit of the registry.

A clear purpose and well thought out design will drive essential decisions throughout the registry lifecycle. The data ascertainment should be well defined and relevant to meet registry objectives. The governance and ethics laws and regulatory requirements should be self-explanatory, and if they are not, here Nancy Dreyer discussed them earlier this morning.

When extracting and analyzing data from multiple registries, the original registry purpose and objectives should be considered to ensure the integrity and validity of the analyses performed and to prevent inaccurate conclusions to be inferred. For certain registries or in certain circumstances, there are some additional principles that may apply.

First, the thought here is that entities funding a registry should have access to their own raw data in order to evaluate and understand areas

for additional research and development to improve their products. Patients also benefit from such improvements. And, second, all stakeholders should be involved in determining the topic for study as well as the study design, planned analyses, and results reporting.

This slide lists some additional points for consideration when designing registries for use in evidence appraisal. The medical devices and diagnostics space has a wide range of device types, and some require very different approaches. Cosmetic devices, for example, that are not generally insurance reimbursed cannot rely on claims data as a valid data source. As such, one must rely on physicians and patients directly to ascertain relevant data.

Over the past two days of meetings, several speakers have addressed the importance of operator skill level and learning curve. Adequate training is absolutely critical, especially for the more complex and intricate devices. I want to reemphasize a key point in the AdvaMed principles, that is, the importance of designing a registry with a focus on addressing very specific questions. As we are all aware, there are numerous examples of studies with lengthy questionnaires that are not well focused, and many of them have very poor compliance.

Lastly, the statistical analysis plan should address potential confounders and other known biases as well as the most appropriate statistical methodologies while also acknowledging limitations of the data.

As a registry example, this slide was drawn from a presentation by Dr. Rod Cooter that quotes some lessons learned from the Australian breast device registry experience. In brief, Dr. Cooter highlighted that an opt-out approach can lead to a high capture rate. Similarly, Dr. Graves stated yesterday that among over 800,000 patients enrolled in the Australian National Joint Replacement Registry, only 26 patients have opted out, which is approximately a .003%.

Some other key points that Dr. Cooter mentioned are as follows: clinical involvement is absolutely essential, the funding models must be transparent and sustainable, and lastly, Dr. Cooter reaffirmed the importance of aligning to a minimum dataset and analytical methodology in forming international collaborations. In fact, the Australian breast device registry has a minimum dataset that is two pages in length, the front and back of a single piece of paper.

By addressing the AdvaMed principles and thoughtfully applying those other key considerations, I think that well designed and thoughtful registry data should be considered as a useful data source for addressing certain post-approval requirements. And recognize that real world experience from registries can inform practice guidelines resulting in practice improvements, identify early safety signals that prompts further evaluation and validation against other data sources, and enable prompt action in response to emerging safety issues.

Ultimately, registry data can be a useful source for evidence appraisal throughout the total product life cycle. And I thank you for your attention.

(Applause.)

MS. KUHNE: I'm going to give you another industry perspective on the use of registries. And, first, I just want to say that I am pro-registry, but a lot of the information that I'm going to present is -- has to do with limitations and some concerns of industry. I just wanted to make that caveat first so it doesn't come off as if industry is negative and against the use of registries.

Currently we think about the medical device development and evaluation as more of a linear approach. With product design, the pre-clinical study -- I'm going to have to put my glasses on. I cannot see my own slides here. Sorry. From the design, the pre-clinical studies, the pivotal clinical study, FDA approval, and then once we have FDA approval, we may have one or more postmarketing requirements: postmarket studies, MDR reporting requirements, 522 studies, other FDA discretionary studies, and other surveillance activities, and of course now registries.

So thinking about this in a more integrated approach -- and that's why I had pulled registries out on this end is that I think registries can provide a feedback loop and can be used to make the pre-approval cycle as well as has already been discussed by a couple of the other speakers this

morning. Not only in terms of expanding indications, providing support for modified devices, but also the knowledge gained during the registry planning and implementation may also help in developing better pre-approval studies.

The world of possibilities in registry data, again, can be used to support the infrastructure to conduct post-approval studies currently, support expanded indications, modified devices, reclassification petitions, and better pre-approval studies.

Now, I've jumped 15 or 20 years ahead, and I've already taken out the post-approval study phase from the total product life cycle diagram here. You start with the design, but instead of a linear approach, it's a more integrated approach. You still have the pre-clinical studies, your pivotal trial, you get approval. There may be still some post-approval conditions such as retrieve all information to identify and evaluate or characterize modes of failure for certain devices, primarily implants. Then we have registries.

So that said, there are still come concerns about using registries especially now in the -- well, I call it transition phase where we are just building up to be able to use registries in years in the future to support the surveillance activities, but now there's a transition period. So currently I think we have a tendency to -- we have the IDE study, of course, to study for device approval. And then we have -- after approval we have the continuation of the IDE study.

So you're collecting the data elements during the IDE, and then

post-approval you're collecting those very same elements in the post-approval phase. And then on top of that you may have an order to conduct some post-approval studies. And now on top of that we have registries. And I say now on top of that, again, because we're not at that point where we have registries broadly implemented and being able to use that for surveillance activities.

Things to consider in terms of being able to use registries and postmarket data for improving the pre-approval cycle is that real-world use may lead to -- you have off-label use. You have protocol deviations if the registries are associated with post-approval protocols, so there needs to be an alignment between -- it's a very pragmatic approach to making the pre-approval process more efficient. But the Office of Surveillance and Biometrics, Office of Device Evaluation, and the Office of Compliance all need to be aligned and on the same page regarding this.

And also there's some considerations regarding just typical post-approval reporting requirements, MDR requirements, and what I mean by this is the timely information that sponsors can retrieve from registries to be able to meet these reporting requirements.

Other things to consider especially in this transition phase is the relationship of ongoing post-approval studies to the registry. Again, we want to avoid that type of layering where the registry is just placed on top and is another requirement on top of the post-approval studies that are

already in place. Also have to develop and consider best strategies to incentivize physicians and patients to participate in registries. We've heard about having the physicians have us be part of CMA, and I think that's -- or CME -- and that's an excellent -- I mean that's just brilliant to incentivize physicians.

Patients, we've heard Anna talk about this morning about concerns that patients have potentially about participating in registries and those fears. So we have to make sure that there's good education and also good incentives to want physicians and patients to participate long term. I think a lot of times people are very excited in the very beginning of the initiation of studies, the initiation of registries, and then as time goes on, that excitement sort of wanes.

And then the depth of data collection. Again, we don't want to layer on the same data into a registry that we're collecting by other means. And so, we need to identify the research questions very carefully and make sure that it's targeted to what we want to get out of the registry versus information and data that's already being collected by other post-approval studies or by the pre-clinical study.

And sustainable business model. Funding, of course, that's important in any project like this. Data access, Dr. Dreyer talked about this morning, so there's no reason for me to elaborate on that. Data analysis in reporting -- concerns about having access to the data, reporting requirements

that may be not so much requirements of the registry, but maybe if they're linked in terms of post-approval requirements, that the sponsor will need to have access to data to meet those reporting requirements.

And then insuring privacy of all: patient privacy, physician confidentiality, and confidentiality of manufacturer specific data, proprietary information.

In summary, there's many possibilities to fully explore the potential of registries. They can play a much larger role in the total product life cycle leading to not only a more efficient pre-approval process, but also to faster approval of better devices. Collaboration with FDA and other stakeholders is key to making this happen. We need to strategize wisely and skillfully plan implementation. Think big. Dream big. Do big. And with everybody working together, we can do all the heavy lifting to reach the goals of having a better postmarket surveillance system in the U.S. Thank you.

(Applause.)

DR. BARBER: Thank you for the opportunity to share the American Urogynecologic Society's experience in developing the Pelvic Floor Disorders Outcome registry or PFD Outcomes registry. This is a registry in development, so it's probably better to say I'd like to share lessons we're learning -- and I'm certainly learning lots today -- and also some of the unique challenges in our disease base that we anticipate going forward in developing this registry.

Pelvic floor disorders are a group of conditions that include urinary and fecal incontinence in women as well as a condition called pelvic organ prolapse, which includes prolapse of the uterus, vagina, and other pelvic organs out the opening of the vagina. It affects as many as 30% of women in the United States at varying degrees.

Because this is not joints or hearts, I thought I would spend a minute or two to explain the disease state so that we can understand some of the challenges we're facing.

On your left is a picture of complete vaginal prolapse, and I apologize for the graphic picture. I thought many of you might need a wake-up in the middle of the afternoon. This is an extreme case of the disease, but as many as 6% of women will have symptoms of pelvic organ prolapse, and one in nine will have surgery for prolapse or one of its related conditions at some point in their lifetime.

The non-surgical options for treating this condition are limited. They consist of basically devices inserted in the vagina to hold things up, so most of the treatment is surgical. There are a number of approaches to surgery. For decades surgeons have used surgical mesh to support the vagina, basically resuspending the vagina after it's prolapsed from an abdominal approach. And then in about 2004, commercially available devices became available for placing mesh transvaginally in order to reinforce and provide better durability than surgical repairs that did not use mesh and take

advantage of the transvaginal approach, which improves the patient experience, recovery time, et cetera.

There are approximately 300,000 surgeries for prolapse performed in the United States each year. Two-thirds of those are done without a device implanted. They're done with what's called traditional or native tissue repair, essentially sutures and reconstructing the supports of the vagina. A third involve implantation of a device, typically synthetic mesh. Two-thirds of those are by one of these transvaginally placed mesh devices, and another third is abdominally placed mesh, a procedure called sacral colpopexy.

Because of this multi-faceted approach to prolapse, we've approached our registry as a disease specific registry rather than as a device specific registry so that we can provide information on comparative safety and comparative effectiveness on the various approaches.

On July 14th of last year, the FDA issued an updated public health notification about transvaginal mesh for prolapse in which they indicated that severe adverse events with this particular approach are not rare. The most common adverse event is a mesh erosion, which I showed you in the second picture, and that the outcomes were not necessarily to have been shown with current data to be superior to non-mesh repairs with the exception perhaps of one segment of the vagina, which is a prolapsed bladder, so that there is some weighing risk and benefits. The other thing

that was noted is that we have very few studies that go beyond two years. Many of these devices are implanted in women in their middle age and may have them for 20, 30, 40 years.

This slide shows a bit of the timeline of the commercialization of these devices and when studies were first performed. And as I mentioned, the first generation devices were introduced in 2004 and 2005. We saw the first study in humans a year or two later, and the first randomized trial was four years after introduction for two of our most popular devices.

Second generation devices, which include different method of delivery, were introduced around 2008 and cleared and marketed at that point. It was four years before we had our first study and literature on these devices, even though they had been implanted in thousands of women over that four-year period of time. And we have yet to have a randomized trial for these devices. And there are many people -- there are many factors that can be blamed for that, but this is a Class II device that was cleared through the 510(k) process, and it's safe to assume that that didn't serve us adequately.

Last fall the American College of OB/GYN representing 40,000 general OB/GYNs and the American Urogynecologic Society representing 1,500 specialists introduced a committee opinion where we talked about many of the things it sounds like were talked about in the previous days about the importance of surgeon training and patient selection, but we also advocated the development of a register for surveillance of current and

future vaginal mesh implants.

On January 4th of this year, the FDA issued 522 postmarketing surveillance studies for transvaginal mesh devices and asked for 36-month data of adverse events: revision, resurgery, quality of life, and effectiveness. Unlike many of the conditions that we've talked about, we do not -- this condition doesn't have hard outcomes. It's a quality of life disease, which does make it a challenge to assess outcomes over time.

The FDA indicated in the 522 orders that a multi-sponsor registry could be entertained by industry, and AUGS volunteered to serve as a host of a multi-sponsor registry. And since January and really over the last eight months, we have been working hand in hand with now five industry partners with the FDA and many other stakeholders to develop this registry. AUGS and the clinical leaders have been serving as really experts on content and design and implementation. AUGS is serving as the host of the registry.

In addition to the industry partners, FDA has been involved as well as the American College of OB/GYN, NIH, as well as urology colleagues who also implant these devices. We've developed consensus on data collected and outcomes. The industry in their studies will be using the shared data of tissue control group in order to decrease cost and maximize efficiency. We've also developed a shared non-surgical or pessary control group in order to meet the 522 order

Our objectives for this register are multi-fold. Certainly

meeting the 522 orders for industry is one goal because they are sponsoring the registry. But the needs of our society members is to be able to track outcomes, individually and as a practice, and for quality improvement. So our objectives for the registry are to evaluate the effectiveness, quality of life and safety associated with all surgical options for prolapse; to assess the effectiveness and quality of life associated with non-surgical management of prolapse; and then also to provide a framework or an infrastructure so that clinical studies can be done within the registry, including industry sponsored studies to fulfill the FDA's 522 request for current and potentially future devices.

To meet that goal, we've developed the registry to be flexible and have various levels of participation. We have a universal dataset, what we're calling level one, with the goal to be again a minimum dataset that the busy clinician can use and track their patients over time with a big emphasis on quality improvement and quality assurance. We've also provided level two or an expanded dataset for larger academic centers who are already collecting and have an infrastructure to collect more data so that they can do that within the registry. And then our third level is study specific data collection where industry will run their sponsored studies to meet their 522 orders.

What are the challenges we've encountered and how are we thinking about moving forward? One challenge we've had as a professional

society is frankly collaborating with multiple industry partners who are competitors to each other and have different goals and aims going forward, both in terms of funding, design, outcomes, and other things. This has become an extremely collaborative effort and been a very positive experience. At that beginning, that was not the case, and it took a lot of time and getting people to the same goal to get there.

The other challenge we have is outside of the 522 studies where industry will be paying sites to participate, how do we encourage surgeon participation? This is not a mandatory requirement, and we don't have a CMS requirement to do this. And so, this will be a challenge. As I mentioned, there are 40,000 generally OB/GYNs, many of which do prolapse surgery. Probably they do about half of the prolapse surgery whereas the 1,500 sub-specialists do about the other half. So how do you get the busy practitioner to participate?

We are hoping to incentivize them by including quality measures and quality measures that will meet PQRS requirements. We also have published guidelines for credentialing for mesh implantation, that surgeons be required to do internal audits and report those annually. And we're hoping people will use the registry to do that. We've also been in touch with our board in order to use the registry potentially for maintenance of certification for our subspecialty as an incentive for people to participate.

The other challenge we have is long-term patient follow-up.

It's not generally clinical practice for surgeons to follow their patients for three years. And the outcome measures we need are not hard outcomes like death and other things that you could use claim data for. They required patients to fill out questionnaires, and they require pelvic examination. So to encourage long-term follow-up is going to be a challenge for us.

The other challenge we have is that when patients have complications -- and, for instance, with transvaginal mesh, mesh erosion has been associated with as many as 10% of those implants -- we know from our data that patients often go to other surgeons and don't come back to the surgeon who implanted it.

So one way we're hoping to improve our long-term patient follow-up outside of the 522 study and within the general registry is to use electronic patient-reported outcomes with regular e-mail contact and reminders to patients over time. We're using the Outcome/Quintiles platform, and they've got lots of experience with that, and we're hoping that will help.

The other challenge we have is there's multiple devices. There's 88 orders that were issued for this, but not all of them will forward with studies. There are also multiple indications, and prolapse is not a cookie cutter stent in a -- there's lots of variations, including various departments, that will make it challenging with analysis going forward.

And then the last challenge we have is the generalist and

specialist. The specialist will be more motivated probably then the busy generalist to participate in the registry. And we're hoping, with marketing and many of the other things we talked about, to include as broad participation as we can, but we'll have to see. We are hoping to launch the registry the first quarter of 2013.

I thank you for your time, and I hope to continue to learn lots. And if any of you have good ideas to help us be more successful, I'm happy to hear them. Thank you.

(Applause.)

DR. PUSIC: Thank you, and good morning. As I said, I'm Andrea Pusic. I'm a plastic surgeon at Memorial Sloan-Kettering Cancer Center. I'm also Chair of the Clinical Trials Committee of the American Society of Plastic Surgeons. And my comments today will reflect the views of the American Society of Plastic Surgeons and the Plastic Surgery Foundation.

I've really enjoyed the other speakers' comments. We at the American Society of Plastic Surgeons are very early in the process of developing registries, and while I'll be talking about our preliminary experience with disease and device registries, I think Matt's comments about the challenges and JoAnn's comments about the concerns about inefficiencies and costs are very well said, and I very much would look forward to learning from other members on this panel in the discussion.

As a starting point, whether breast implants are being used for

cosmetic breast enhancement or for reconstruction after mastectomy, breast implants can provide important quality of life benefits. And as I work at a cancer hospital, I see evidence of these benefits every day when I come to work. However, that said, safety is clearly a tremendously important concern where breast implants are being used. And with this, the implants were taken off the market in 1992 only to come back in 2006.

So given this and the fact that there have been these concerns, and also the fact that we still don't have a clear understanding of safety and effectiveness of breast implants in the long term in the real world experience, national efforts have been increasingly turning to registry development.

And I'd like to start by talking a little bit about our disease-based registry experience and this is very preliminary -- our preliminary experience. But I would say I think that this is -- although it's very preliminary, I think this will be an example of something that is working well.

Almost two years ago, there were reports of a rare cancer that was being noted in association with breast implants, so anaplastic large cell lymphoma, or ALCL. And even though we -- and I say we being the ASPS and the FDA -- recognized that this was very likely a very rare event with a likely incidence of about one in a million, we also recognized that there would be some very important questions that would need to be answered around this disease.

So questions like, which women would be most at risk? How

was the best diagnosed clinical course? How might it be treated? What was the true incidence? And particularly important, what is the association? Is there causation? These kinds of questions around it.

So just over a year ago, the ASPS entered into a cooperative agreement -- it's a cooperative research and development agreement or a CRADA -- with the FDA to collaborate in developing a breast implant registry for ALCL patients. So this registry is called the PROFILE study for Patient Registry and Outcomes for Breast Implants -- it's a long name -- Anaplastic Large Cell Lymphoma Etiology and Epidemiology.

It's very preliminary, but we have now -- I'm co-PI of this register with Cara Krulewitch who's here today from the FDA, and we now have IRB approval, and we are open for business to collect cases on patients worldwide, the women presenting with an ALCL-associated breast implant -- ALCL in association with a breast implant.

So from here I'd like to move onto our discussion about devices and disease, and I'll use our experience with ALCL moving forward in terms of how we then migrated into a discussion around a device-based registry. So as it's been said, device registries can play an increasingly important role in bridging this gap between clinical trials and clinical practice. And specifically understanding the real world clinical experience and also in the long term, which is particularly an issue with breast implants. We currently don't have a national breast implant registry, but this is something that we're working

towards.

What we learned from the ALCL experience is that there was a tremendous opportunity for successful collaboration among stakeholders. Clearly the safety and effectiveness of breast implants is not just a concern for the FDA and for the implant manufacturers. It's our concern as surgeons. It's the concern of the other women's healthcare providers. It's certainly the concern of patients and patient advocates. But what we learned from the ALCL experience was that we could work together and we could identify our common goals and relatively quickly put something together that will provide us with the answers to the questions that we had identified.

So with this in mind, in August of this year, the ASPS and the FDA amended the ALCL CRADA to explore the development of a national breast implant registry for patients receiving implants in the U.S. And so, a primary goal at this stage of the project is really to engage stakeholders in the developing of a comprehensive plan for implementing and sustaining a multipurpose national registry, and sustaining being talking about issues around business models and about the different needs of different stakeholders and all the challenges that Matt has mentioned as well. And that's why I welcome these thoughts because we're at the very beginning of this process and learning as we go with that.

What we anticipate in terms of the registry is a registry model where we have a minimal dataset, but post-approval studies being embedded

in that moving forward. And so, it would be for streamlining that data collection process and minimizing as opposed to increasing the -- and increasing the efficiencies. And also collecting data from ASPS member surgeons that have not traditionally been engaged in the post-market approval study collection, data collection.

Just in terms of our highest priorities -- and this is really my take home message today in terms of from the ASPS perspective looking at as we move towards a registry. And so top priorities are to ensure patient safety through an enhanced long-term device surveillance. We are very much as plastic surgeons interested in the real world experience and improving our understanding of long term safety, so both the long term surveillance and real world experience.

Obtaining high quality clinically meaningful patient-centric outcomes data. We're looking for data that will help surgeons be able to actually improve outcomes, so that's why the issue about clinical meaningful data is important to us. We're looking for data that we can also then provide back to our patients that will allow them to participate more fully in shared medical decision making.

From our perspective, it's not enough to be looking for the rare events, but what we're also interested is having a really robust, clear understanding of the common events and the common outcomes and expected outcomes and in such a way that we can provide that information

to member surgeons to improve techniques, but also to patients to improve choice.

We're particularly interested in a patient-centered approach in terms of patient reported outcome measurement, and we do have an experience already with having electronic patient reported outcome measurement developed in our national registry, our procedural registry. And we're hoping that we would migrate that into the development of this registry.

And then finally, to facilitate the safe and effective entry of new device technology into the U.S. market. Breast implants need to continue to evolve and innovation needs to be able to continue so that we can continue to offer better solutions and better surgeries to our patients. And this is effectively when I go to the OR every day, that's what I'm hoping to do, is put in a better implant next year or put in -- or know what techniques will lead to better success and particularly from the patient's perspective.

So I'm going to leave off that and pass to the next speaker. Thank you.

(Applause.)

MS. BROCK: Good afternoon. Now, it's afternoon. I'm going to try to keep this a little bit short because I know we're all probably grumbling in the tummy. My name is Janet Brock, and I'm here to give the CMS

perspective. I am the Director of the Division of Operations and Information Management in the Coverage and Analysis Group.

So what I'd like to talk about is particular to how CMS is using data for coverage and by proxy payment determinations. There are lots of ways that CMS uses data. I'm not particularly going to talk to you about demos. I think you may have heard from Rick Gilfillan yesterday if you were in the room for that. We're fortunate to be an agency with a rich treasure trove of data. We're just learning really how to use that data.

I love this quote because I think that everyone in the room and those who are listening in via webcast are a bit like Columbus. We're all sort of standing on our own shore, we're looking out there, we know there's something to connect to. We're just trying to figure out the way to do it.

So I put this here to remind myself and to remind us all that we don't have to build one registry to answer all the questions. There are ways that we can connect within each other. And I think we've heard that today at the panel, that infrastructure is a very important piece of this and that we have choices to make, balances to consider, and that's what I'm going to talk to you about today.

So why CMS? I mean, after all, we're not a regulator of devices or drugs. We lean on FDA for that. We're a payer. What do we have to do with the total product life cycle? Well, we have a charge to pay for only those things that are reasonable and necessary.

And it's an interesting charge because it sort of knocks everything out of the park unless we can hit that reasonable and necessary threshold. And we've approached this in several different ways over the years, but we've always tried to maintain that first FDA does their part. We know that something is safe and effective per the FDA, and then we look at whether it's reasonable and necessary. It's a very different question.

And there is no definition per se -- I wish there were -- of reasonable and necessary, but the way that one can interpret reasonable and necessary based on our case law, if you will, our decades of decisions is that reasonable and necessary means to us adequate evidence to conclude that the item or service improves clinically meaningful health outcomes in the Medicare population. And we've leaned on evidence-based medicine for the last decade or so, since about 1999, to really help us put some structure to those determinations.

And the thing I like, recently Dr. David Eddy was in an article where he was having a conversation with Sean Tunis. A fabulous article. I recommend it highly. One of the things he reminded us about evidence-based medicine is that there are two parts: there's evidence and there's judgment. And I think we've heard a lot of that at the table today, that everyone at this table is using evidence and registries as tools to make judgments: clinical judgments, policy judgments. But there are two parts here, and finding the way to marry those things is really an art and a science.

Where do we go from reasonable and necessary and what do we do with this evidence-based medicine framework that we use? I like to think of this as jumping first and building our wings on the way down because when we started using evidence-based medicine, we had few types of determinations that we would make. We'd either cover something or not cover it, or kick it to our contractors to make the decision. Those were the three types of decisions that CMS would make.

And we've had to evolve considerably because the determinations that we're making today are much more nuanced. The types of evidence that are given to us -- and we all know the hierarchy of evidence, so we're looking at evidence of different strength -- are in many ways incomplete. So we have to be able to balance -- there's that word -- the things that we want to be able to do for Medicare beneficiaries with what's available to us in evidence. And I think we heard this morning about the TVT Registry, and I think that's an excellent example of this.

Obviously, there's lots more that we want to know. There's things we want to learn. You can read our decision memorandum to understand those things that we'd like to learn about the patient experience with TAVR. We do not think that it is prudent to wait until those questions are answered in order to confer coverage for these types of devices.

This is what you see in this slide. We know that we're never going to have the perfect answer. We may never have the perfect evidence.

So one of the things we had to do is develop a way that we could make the judgment based on what we had in front of us and move forward. And this is where I see registries coming in for CMS and in fact for all of us. I think we all make these judgments, and it's important to recognize them.

The way that we've made these judgments is coverage with evidence development. You've heard about this, so I'm not going to spend too much time on it, but this is the way we made the TAVR determination. There have been 13 or 14 similar determinations made by CMS using this paradigm, and what we tried to do with coverage with evidence development is acknowledge that the evidence is not complete in the way that we might need it to be for our population.

Remember back to our charge: reasonable and necessary, clinical outcomes, Medicare beneficiaries. Something's missing, and we acknowledge that, but that we see enough there that we want to be able to learn more. And in many of our coverage with evidence development decisions, we've asked for more either through studies or through registry participation as you've heard about with TAVR.

What we hope to gain with the registry participation is really getting to a place where we understand the appropriateness of the use, we look for evidence that can help confirm our judgment that we've made the right decision or perhaps need to revise the decision that we made, and informed medical decision making. And this is where I think we see ourselves

as good stewards and good citizens because this information is helpful for all of us, not just Medicare.

The value of administrative claims data in the total product life cycle. We've heard a little bit about this this morning, that claims data, it's got issues. Well, that's true because it's not the real world. It's an approximation of the real world. After all, this data is sent to CMS for the purposes of payment, so it matches what CMS usually has asked for for the purposes of payment.

And we've based this all on coding and DRG and things of that nature, all these wonderful things that we all know about so well. They all have limitations. Even the ICD10, which I'm working on diligently, which will be delayed but that's okay, has limitations. Nothing is quite as good as what you would get if you sat down with the doctor and said so what did you do? What did you do in the ER? And they tell you. Knowing we have these limitations, what good is claims data?

Claims data can give us missing pieces on the puzzle that you're not going to get necessarily out of even the best designed registry. Registries, as we've heard, should be designed with protocols in place, with research questions that you want to see answered, and that's absolutely appropriate and absolutely essential in fact. What we don't know is what we don't know.

What we find sometimes in claims data that sets us off on a

course of multiple hypotheses is we see things that we didn't expect. And this is valuable. There is something there that's important to look for. This is why the connection to postmarket surveillance is so rich. You find indication creep where you didn't expect to see it. You find out what real world looks like in patients who are really hard to manage. Poly pharmacy. They have multiple comorbidities. They're all over the map in compliance. This is the kind of stuff that's really important, and you really can't build a registry to answer the question you don't know to ask.

With that I say, yes, claims data has its own limitations. I think that we can overcome those limitations by bridging that gap, by building the channel of thought, as the initial quote said, to the other types of data that are out there. I think it makes it much more complementary, more rich, and I look forward to us having conversations about infrastructure because I think that that's the start. Thank you.

(Applause.)

DR. FRANKLIN: I'll get started because I know we're all hungry. Again, I'm Pat Franklin from UMass Medical School, and I'm here to talk to you about the AHRQ-funded infrastructure that we're building, which includes a national network of surgeon offices, patients, and data collection to evaluate comparative effectiveness research, so this is indeed postmarketing in total joint replacement.

Our paradigm, just to tell you, FORCE stands for Function in

Outcomes Research for Comparative Effectiveness in Total Joint Replacement. That comes from the RFA. There was an initiative that AHRQ asked for that kind of comparative effectiveness infrastructure.

And what we proposed is that we wanted to establish a national cohort of over 30,000 diverse patients from more than 100 diverse surgeons representing all regions of the U.S. with varied hospital and surgeon practice settings. It is not that 100% of the U.S. It is a sample of the U.S. But the intention was to go into it in a very knowledgeable way about the diversity that need to be represented if we were to evaluate the use of the total joint replacement implants.

We also proposed because this is based on a patient-centric paradigm, that the annual assessment of outcomes would come from the patient with patient-reported pain and function because those are the reasons patients have the surgery. It is a choice. It's a progressive chronic disease that they're treating. It's osteoarthritis. There is no cure. Surgical care is effective, but not mandatory. Secondarily we'd be studying adverse events and revision, which you've heard a lot about today.

For purposes of time, I'm not going to describe the whole study or its design. I'm going to emphasize these three unique features that differentiate it from the traditional Swedish hip registry, for example, that's 100% payer.

First, we have a diverse national cohort of patient, not

implants, for surveillance. Second, we have broad patient-centric outcome metrics, and we're going to talk about that. It's beyond revision because people do live with degenerative pain after an implant that's not revised and it has failed from our perspective. And, third, we will evaluate total joint replacement benefits as well as risks because we're interested in the whole picture. It's not an all-or-nothing scenario in our minds.

First, what do I mean by a diverse national cohort of patients? General orthopedic surgeon trainees are trained to do total joint replacement. They are not conducted -- the majority are not conducted by academic centers, by specialists; they're conducted every week in general orthopedic offices. Two-thirds, 67% of our surgeons are community based. They are high and low volume surgeons. They're the type that do one a week, 50 a year, one week a knee, one week a hip. They're urban and rural. They're private, public, and HMO insurance. There are HMO participants, including Geisinger et al., people participating right now. We have all major implant manufacturers included in this sample.

The diverse national cohort of patients is critical because the fastest growing subgroup of users of total joint replacement are those under 65. So while we'd love to use the Medicare data uniformly to learn about this, 40% currently are under 65, and that's growing rapidly. We went out there saying we needed to know more directly from the patients with the diverse group, and we chose to use a consent. We actually used the

Women's Health Initiative in our design because it's a model of longitudinal tracking. And then the UMass site had 95% retention at 10 years, so it is possible with PROs, with patient-reported outcomes. And we built on that. We borrowed very generously from methods to say how we're going to invest these patients and maintain them over time.

I want to emphasize the last sentence. We know patients change location. They move. They change hospital. They don't go back to the same hospital necessarily a lot of times for revision. They don't even go back to the same hospital -- I'll tell you some data -- for their post-op events. They change insurers and they change states, so that's a critical issue to think about.

I show you this map because these are the current -- in green are the current enrolling sites. We start with five core clinical centers that are high volume: UMass; Connecticut Joint Replacement Institute, private practice but very high volume; University of Rochester Medical Center; University of Maryland urban; we wanted urban in both the northeast and in the southwest, so Baylor College of Medicine.

Now, I wanted to pause here because I'm not going to talk about methods to just say these community surgeons -- if you're doing one a week, we're not going to put a research nurse in the office. It doesn't work anyways. We want to make sure that we're getting -- it's not a knocked out. It's a knocked in. You have to sign consent, but when they join, do they agree

that at the same time they hand the patient their consent for surgery, they get a consent to participate in this study?

And we call them within 24 hours. The centralized coordinators review the consent, describe the process of participation, the value for them, the value for their surgeon. The surgeons love it because it helps. We love it because it's better data and it has a denominator. It's really been a win-win.

And this is just to show you that it's accelerating. This shows you on the Y-axis that in the second half of 2011, we had just been funded. We started with our five core sites, but the last eight months in 2012 we started adding the community surgeons, and now there are over 6,000 active participants in this study, over 109 surgeons. And we have people referring their friends, and it's been nice to see, but they're on the waiting list because we need representative practices.

The second part that I want to emphasize is that this was patient-centric from the design. Traditional total joint registries focus on implant failure in surgical revision, and that is a very appropriate and devastating endpoint, and that should be honored. However, in this case what we wanted to do was to say that patients choose surgery for pain relief, number one, and two, for improved physical function. And those are their primary goals. It's critical that we address these when we're studying their outcomes.

We secondly said that there's really interesting information

emerging that pain and poor physical function is an indicator of potential implant failure. So how do we say that? That unusual patient pain preceded the metal-on-metal failures. There are people and patients telling us there were concerns and problems with their implant.

Second, the New Zealand registry, which is total -- they're 100% country registry and does use an abbreviated PRO -- reported in their 2011 report that significant pain and disability at six months after surgery significantly predicted two- and five-year implant failure. We think now that this not just an endpoint. It's a surveillance mechanism for understanding the process of care.

These are real data from the patients that are at least six months out in our study. And the details are not the point. What I want to point out to you is on your left is the pain graph and on the right is the function graph. And the dotted red line is the distribution of pain on the left and function on the right before surgery. The green is the rightward shift or improvement after surgery at six months. The large thick green arrow is showing you that the mode or the mean is at 50. That's remarkable. That's the norm based average in the PCS physical function and pain scores in the SF-36.

That's why the procedure is so powerful is that patients can be back to normal pain relief and function, but they don't all go back. Look at the left tail, the distribution. That's where they're still hovering where they

started at the red arrow. Those are the patients that we will obviously be actively surveilling.

The second part is that if we're going to the patient and we know that they travel, we want to ask them about postoperative events. So early on we need to understand what's going on. We found in our first part of our cohort that 38% of hospitalizations and day surgeries for those that had them after surgery were not in the indexed hospital, and almost 50% of ER visits. They go to the closest ER. It's not where you had your surgery.

So, secondly, so this is another reason we said okay, if 40% aren't going to be in the Medicare claims data, we need to find out what's going on. So we ask it every time, did you go to a hospital, an ER, your surgeon, or have any other concerns with your knee or hip implant? We validate that actually with Medicare claims and surgeon reports. And I'm going to tell you just in one slide how we do that.

This shows you that we have three inputs to this registry: the patient; the surgeon, the M.D., and that's in their ambulatory office not in the hospital; and then the OR. The patient will tell us at every time point their pain, their function, and if they've had any events. That generates our call to the office for the charts with uniform reviews -- hopefully electronic, but if not paper, we'll take whatever we have -- and using uniform definitions for post-op events.

The majority of the DVTs, infections, they aren't in the hospital.

They go home after three days. It happens at varied times post-op. It's in surgeons' offices. And then we validate that with clinical data, and we're also using -- we always go back to the indexed hospital to get the OR data from the initial implant and then any follow-up surgical data.

The important part here that I want to point out is that we impose the time periods, so if it says six months, it's because we either e-mail them and deliver their web-based survey or write to them with their paper scanned surveys because they've chosen the mechanism of reporting and at those intervals. We don't ask the surgeon to ask them to come in at six months or ask them to come in at 12 months because that changes practice. It's not what happens in the real world. Actually, we learned that the hard way.

The last point I want to make is that we really feel like we were in this to evaluate benefits as well as risk. So while we've talked a lot about the failures, we think that it's important that we can profile, for example, subgroups of patients with the optimal post-total joint replacement pain relief and functional gain. We can flip it and do the sub-optimal as well, and we will. We also think that it's critical to be able to do these evaluations in a hierarchical approach from patient factors through comorbid conditions, clinical factors, physician and hospital factors, and implant design. So it's not just an implant registry or an implant database, because we've heard a lot this week about practice is in the hands of a practitioner, in a setting, in a

hospital, in a team, and in the patient's self-management.

And this is just to quickly show you in our profile in one slide, there are things like I have low back pain and left hip pain. That will be reason why I'm not walking well, even though I had a successful knee surgery. And these aren't exactly variables you're going to find in the administrative claims data and you're not actually going to get BMI.

So there are critical predictors that we think need to be collected. However, having said all of that, we don't want to do this without interoperability so that we use the AJRR's definitions of their lot and catalogue number for implants. And so, that's the way we think it should be, and we'll share these implant data with them so that surgeons aren't making decisions about what do I do, that we'll help process that information for them so the implant will be there as well.

What I didn't talk about in this slide is what we're giving back to the surgeons. It's not money. It's data. They really welcome it. They are being asked by their insurance companies about their outcomes, their post-op events, the website for them to be able to look up their own patients' scores for their physical function and their own adverse events is going up in the fourth quarter of this year.

This is my last slide to say that we wrote this application to say that we have a public health goal. We want to be an independent, unbiased expert data collection and analysis infrastructure that will be able to ask

research questions to define best total joint replacement practices and outcomes for the optimal pain relief functional gain with minimal adverse events and implant failures.

Thank you for your attention.

(Applause.)

DR. MITCHELL: Thank you to Pat, and thank you to all the speakers for some really informative talks. Before we go on to questions, I just want to ask Cheryl -- I know she was not a planned speaker -- if there were any comments that she would like to make?

DR. IGLESIA: No. We used our 10 minutes. And the only comment I would say is that early on we are broad specialty. We've got urologists, urogynecologists, and OB/GYNs, and we've come together in something that's a little bit dicey, but in order to make a common goal of improving what we can offer for the treatment of pelvic floor disorders and not just an implant registry. Full spectrum.

DR. MITCHELL: Thank you. I just want to take a few more minutes. I want to take a minute at the end to summarize the discussion for Danica and Tom and their work with implementing the strategic plan, but before we do that, are there any questions from the web or the audience that we can entertain? And I am being cognizant of what time it is. Nothing from the web either?

Forgive me. I'm going to pull this way back up to the 50,000

foot level, but we had a great discussion today. We talked about a variety of things, all of which Danica and Tom and everybody involved in this room is going to have to take into consideration when implementing the postmarket plan.

We've learned that registries have value and need to be part of our future. I guess that's a given. We've learned that they can be both for postmarket questions and also possibly even premarket questions. However, we've heard that they should both be really focused and yet have the opportunity to offer us a treasure trove of information. That's a separation that we're going to have to bridge as we move forward.

We've also learned that infrastructure is critical and really challenging, but building a really excellent base for the registries can make a huge difference in terms of the ability for the registries to actually be useful for an immediate need and possibly needs in the future.

Finally, we've heard lots of great examples of a variety of different registries and what they have to offer and some really key considerations with regard to important patient characteristics as well as important clinical practice characteristics that we need to consider when designing the registries.

Did anyone from our panel like to comment before we conclude? No? Okay. All right. Well, thank you. We've had a healthy feeding of the mind and now a healthy feeding of the body.

Danica is telling me 35 minutes for lunch, so it's 12:56 that means 12:30. I'm sorry 1:30. Thank you very much.

(Whereupon, at 12:56 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:55 p.m.)

DR. RITCHEY: Good afternoon. If you are a panelist for the next session, please come to the front and have a seat. Thank you.

Our first session this afternoon is about optimizing performance and ensuring the best methodologies for registries. My name is Mary Beth Ritchey. I'm an Associate Director in the Division of Epidemiology, and I'll be moderating this session.

We have people from STS, ACC, Quintiles/Outcome, the VA, Harvard, Cornell, and FDA who are presenting in this session. And I've had at least two people already tell me that they only have five minutes for their slides, so we'll attempt to get back to schedule during this session. I'll let each of you introduce yourselves as you begin your talk, and Dr. Edwards, we'll start with you.

DR. EDWARDS: I'm Fred Edwards. I'm a cardiac surgeon at the University of Florida and Director of the STS Research Center.

DR. BRINDIS: Ralph Brindis from the American College of Cardiology, past president and past chair of the management board and medical officer of the National Cardiovascular Data Registry.

DR. DREYER: Nancy Dreyer, Epidemiologist and Chief of Scientific Affairs at Quintiles/Outcome and senior editor of the AHRQ Guide to Patient Registries.

DR. VAROSY: I'm Paul Varosy. I'm a cardiac electrophysiologist at the VA and the University of Colorado.

DR. NORMAND: I'm Sharon-Lise Normand. I'm a Professor of Healthcare Policy and Biostatistics at Harvard Medical School and Harvard School of Public Health.

MS. REED: I could pretend I'm Art Sedrakyan and I'm an associate professor at Cornell. I'm Terrie Reed. I'm also at the FDA.

(Laughter.)

DR. RITCHEY: You're a lot of people. You have a lot of hats. Can we get Dr. Edwards' slides?

DR. EDWARDS: All right. That's good enough. We'll start there. We've talked a lot about registries here in the last couple of days, and as we planned this, we thought, well, it probably would be good to have a session where we focus on what registries can and can't do. So take a step back and just look at it in that light.

And as you might imagine, my focus is going to be on the STS database and NCDR from ACC. I think most people in the audience recognize that these are large, multi-institutional, mature data registries with a very high degree of penetration across the country. And we think that they satisfy the criteria for distributed data sources as defined in the FDA white paper that was circulated around last Friday. And we know that FDA seeks to promote the development of national device registries. And as we've heard

Mike Mack and others point out today, it looks like the STS database and NCDR are ideal for serving as platforms to develop these registries.

Why would that be correct? What are we doing right? Well, the most obvious thing is we've just got a huge *n*. We have over 20 million patients in these two databases with a ton of clinical information on each one of the patients. And we're talking about academic institutions, private practice, military, VA, so it truly represents a real world experience. And it also is an experience that lets us know that when we focus on these patients, we're not lucky. It's something that is restricted and highly selected.

Now, audited high-quality data. We place a high premium on this. We're very serious about the way that we ensure the quality of our data. We have both internal audits and we have external audits so that we have independent auditors actually going out to the different hospitals. They'll sit down with a patient record and make sure what's in the record is in fact what's in the database.

Harmonized protocols. The first time we did this was out in San Francisco hosted by Ralph Brindis. We make sure that to the greatest extent possible, the definitions that we've got in STS are the same definitions that are used in the ACC database.

And what does that give us? Well, if we look at device comparisons and we look at studies that make comparative effectiveness research determinations from the different projects, what we've got in the

database is essentially a denominator, a control group, a comparison group. And we can drill down to find the clinical subsets that are necessary for the particular study very easily. We can easily establish the filters that'll help us identify exactly those subpopulations.

We've got a lot of risk-adjusted outcomes collected in the database, and I would emphasize the point that Mitch made earlier that we have in place an existing national network. This is a communication network, so that if we need to get the word out to someone and need to get it out promptly, then we've got the system already in place to do that in both of these registries.

Well, where do we need work? And longitudinal follow-up, of course, that's going to be first on the list. And we've talked a fair amount about that already today. I'll talk more about that when we go over the goals.

Capacity to conduct clinical trials. We can do observational trials quite readily. Clinical trials, can we do them? Yes, but it's a quite cumbersome endeavor to do so.

We need to capture nontraditional data. And by this I mean quality of life information, frailty indexes. We recognize the importance of all of these, yet we still don't collect them. And we're not very nimble. If we need to make a change in a database definition or what we collect and what we don't collect, right now we've got to wait until the next version of the

database comes out before we make those changes, so we're not very nimble.

And we need more experience working with the government. We need more experience working with industry. That seems to be something that we're reminded of just about every day. We recognize the importance of it, but the fact of the matter is it's still relatively new to the professional societies, and we do need more experience with that.

Funded research. We've heard presentations by AHRQ, by NIH in the last couple of days, and I'm sitting out there in the audience thinking, boy, we can do exactly that. We can address exactly what they want to devote their attention to. And, yet, where is the funded research? Granted we've got some, but we need to have much more. And funding for the registry itself, more about that in a bit.

Where does this lead us for short-term goals? Well, I think we need to have a continuous link of our clinical data with administrative data, and probably CMS data is the place to start. And Rosemarie and I talked yesterday about this. She assured me that continuous data linking was never going to happen, but perhaps at three-month intervals, six-month intervals, maybe it's the kind of thing that we could make happen.

I'm surprised nobody's mentioned this up to this point. Boy, would it be good to have the Death Master File back again. Think of what a great advantage that would be. We can become more nimble. We can make

these changes to the registry if we develop web-based modules. And that's not a pipedream. That's a reality. We do have a couple in place. And you can literally make changes in the registries in a matter of days or weeks.

And let's just go ahead and establish these metrics for quality of life and frailty and begin to collect them. I think one of the advantages of having a registry like we have is that we don't have to restrict ourselves to the existing metrics right now. We can define our own and define them in a way that's tailored to the population that's in our registries.

Learn the language of FDA and CMS. Absolutely. A week doesn't pass that I don't pick up a new acronym somewhere it seems like.

Work more closely with industry. Pretty obvious. And create these hybrid studies like Mitch mentioned this morning. It's probably going to be an onerous process as we begin, but there's real value in doing that, and it's something we need to focus our attention on.

And establish a presence with the research agencies. We still don't have a way to really let them recognize the value of these registries and how they can fit with their plans.

How about on a more long-term basis? Rather than have the link with only CMS data, which essentially restricts us to patients 65 and over, how about a link with other administrative data so that we can have the whole age spectrum of patients examined that have long-term follow-up associated with that?

Link with EHR. I know that's going to be discussed later on in the panel, so I won't devote a whole lot of time to that.

But I would emphasize the last two bullet points here and the last one in particular. Danica and I did not collaborate on our presentations today, but that last bullet point that you see here is almost identical to one that she presented at our Tuesday morning briefing. And right now as has been pointed out before, we've got a disjointed system. We have a research project going here, we've got something else going there, we're not talking to each other. All of these things are taking place in silos.

Wouldn't it be good if we did in fact have an integrated system where these registries are part of the process with CMS, with FDA, and perhaps with industry as well so that when it comes time to do a study, we don't have reinvent the wheel? We don't have to start all over again. We'll have the infrastructure already in place and smoothly transition into the new project. And that'll be a benefit not only for the government organizations and the professional societies, but for the patients as well.

Thank you for your attention.

(Applause.)

DR. RITCHEY: I do have one follow-up question before we move on. You mentioned a continuous link with claims data?

DR. EDWARDS: Yes.

DR. RITCHEY: And that could mean a few different things, and

I'm picturing something in my mind. But if you could speak to what that means, I'd appreciate it.

DR. EDWARDS: Well, apparently it's a little bit different in my mind, in Rosemarie's mind, in Louie's mind. What I envision and I think what STS envisions is at periodic intervals taking our clinical data and acquiring new data from CMS and then establishing a link. Whether that link is established at CMS or whether that link is established at D.C. or at our warehouse agent, it really doesn't matter. But then you would have not only the periprocedural information, but you would have long-term follow-up information that we could provide to our participants.

And how useful that would be to be able to say, well, yeah, I know I can do this operation and get a patient out of the hospital, but how is he doing a year later? That's the kind of information that we really need in the database of the future, I think.

DR. RITCHEY: Thank you. Dr. Brindis?

DR. BRINDIS: Terrific. Thanks. I'm going to try to see if I can keep to Danica's five-slide, five-minute rule. I'll do better with hopefully the five-minute rule.

I'm here to discuss establishing common data module/definitions. And I will say that this is an incredibly important issue. It's discussed a lot, a little bit this morning. We understand the issue of Tower of Babel related to the English language and other languages. It

certainly holds true in the setting of definitions and it also occurs -- the Tower of Babel -- related to the warehouse standards in terms of the electronic needs.

Fred mentioned the harmonization between STS and the NCDR related to common definitions. I want you to know that we spent three hours and never agreed on the definition of death, so it is a challenge.

When you look at this slide, you can see what's before us. We have many different players interested in this area: research, quality measurement, clinical decision support, population/public health, business operations/administration, clinical data. And if you look at all their different elements, you can see they intersect and have some common data elements.

What we would really like to have is to take multiple single source data, throw it into a box through our healthcare data systems, and be able to churn out multiple uses for such, whether it be for patient care, quality improvement, research, reimbursement, postmarketing safety, decision support, administration and management, public health reporting. This is our goal.

Now, with the ACC through an ARRA grant with NCRI, we've actually started building a full EHR profile that can be used for decision support software, guideline support, and structure reporting. This has been endorsed by CDISC and also HL7. And Mitch again sort of implied a little bit on his talk how already a lot of eliminating of duplicative data entering can be

accomplished through this mechanism.

If we look at this model, at least for the NCDR, the goal here is to be able to interrogate the electronic health record and be able to auto-populate all of our clinical registries, and even vice versa where our clinical registries, if you will, typically are episodic hospital based, but through the integration with the electronic records, we can then develop a hybrid approach that can be patient focused or procedurally focused and that of longitudinal care. In fact, Liz Paxton talked very nicely on how this had been accomplished within the Kaiser Permanente system.

Standard elements are needed and common definitions using existing ontologies. These existing definitions have already started to occur. We call them the ACC Top 100 in terms of cardiovascular domain. They again have been approved by CDISC and HL7. They have taken common definitions from cardiovascular disease and been able to, one, get an English definition that's the same and already incorporated into the electronic aspects of the record. Actually, this 100 is closer to 200 already.

Utilizing from this pyramid, other sources include our work with STS and our harmonizing data elements, the ACC-AHA data standards, and harmonizing data elements through our own registries. This slide's kind of complicated, but the concept here is that no matter what source of data, from whether it be patient, physician, research, data groups, or whatever, gets thrown into that box and can be utilized for harmonization of

cardiovascular data, cardiac registries, clinical trials, FDA endpoints in clinical trials, and electronic health records.

Now, where are we? Well, we're doing reasonably well, and that harmonization has been achieved using these techniques about 90-95% in most of our registries, using contributing sources from the STS, CDASH, our data standards, and others. This is, for example, what is actually exported to CDISC and EHR vendors in terms of what has been created.

Where do we need to be in the future? So now, we have developed cardiovascular domain analysis models harmonizing data use cases. We appreciate that you need to be CCHIT certified to meet meaningful use. HLA representation. We appreciate that CDISC is the preferred FDA data submission standard for clinical trials. And these mappings are all occurring.

In the future we will be able -- hopefully, the near future, to be able to incorporate these techniques into our cardiovascular electronic health record in terms of functional profiles, clinical integration, CCHIT certification, our support and guidelines support, structured reporting, and FDA cardiovascular trials data warehouse being the common goal.

Again, our single source into a box, if you will, and coming out for our multiple uses. And actually we're quite proud at the ACC level in that we have been designated by CDISC and HL7 to be the source of overseeing and maintaining the cardiovascular domain here as we expand cardiovascular data elements to meet these electronic needs.

(Applause.)

DR. RITCHEY: Thank you, Dr. Brindis.

Dr. Dreyer?

DR. DREYER: Now, I love hearing about these big structures where everything is planned and disseminated and just have things done. And I feel like I'm your representative from the Wild Wild West. Because I'm going to be talking about using electronic health records as they exist now.

And I need to preface this by -- I probably spent 20 years of my career working with claims data. And we've heard this morning about how deficient claims data are for a lot of the research interests we have, and I agree. But claims data, you know what they are, you know the biases that go into them, you know that they're reviewed very carefully because payments are made by them, and you know what's included and excluded.

I've been working for the past three or four years with electronic health records from numerous freestanding systems that just want to collaborate in research. And you need to know that electronic health records are populated at the will and the whimsy of each individual healthcare provider at the moment. So there really aren't rules that you have to fill out everything completely.

The variation even with the same EHR records between healthcare networks is big. Even within healthcare networks, it's not implemented the same way in each department. Some use notes, some

don't. And there's no common definitions currently for most things that are in there. If it's a fracture, you don't know if it's a simple fracture or a compound fracture. If the device was removed, you may not know why or enough information. That's my introduction.

The premise here is that electronic health data can significantly reduce the burden, and I totally agree with that. We need to know that fully functional multi-purpose interoperable model isn't there yet. Currently, we use point-to-point solutions. You have a problem, you work with a vendor, you get a solution, and you contribute data specific to a research issue periodically. There is some standardized output. These continuity of care documents, CCDs, which are standardly transmitted, and it's so exciting to hear about the uniform device identifiers, so I'm going to skip that part of my talk.

What's working? The EHR works pretty well for an individual. We've heard about access issues and the like, but conceptually it's a great tool for an individual. And the registry, my definition is it's uniform data collection that serves a scientific purpose. And whether you consider it either a means to collect data or a study in itself, it's either a resource for studies or a study, but it's population focused.

What's missing? Healthcare facilities that are part of registries generally use several data collection systems. Many, as I show in this slide, use four or more. There isn't full interoperability. And I'm going to explain in

a minute what I mean by that. And what we need is a standards-based solution for interoperability that's easy to participate, to opt in or opt out, and the most simple data collection we can do so that we avoid duplication of data entry and just focus on what's missing.

Interoperability. What is that? Well, there's two aspects to it: syntactic and semantic. Syntactic is like the plumbing. You can't open the faucet and expect water to come out if you haven't hooked up the plumbing. So that's the way to make a connection. Now, I don't have the analogy quite on the semantic side, but that's can you understand what you get? So when the data -- you get it, do you know what you're getting and what it means?

So we have trying to harvest what's already there and understand it, and then the second part to get the information that you need that's missing. It isn't there in any systematic way. Just think about patient-reported outcomes. How is the pain scale? How is somebody doing? How are they feeling? And we want a system where you can be part of it for minimal cost and minimal burden. So I'm going to show you how it works.

So you can see, this is an example of a forms library from an electronic health record. What happens in the world of interoperability is the patient comes in and you get an alert. Hey, this patient has a condition or an exposure that we're interested in studying. So that's your alert. And then, if you could see this slide, what pops up is it automatically goes into the electronic health record and starts to pre-populate the fields that are there

that are needed for your study.

We got the EMR pre-populating, then we have the continuity of care document also contributing, we're using open standards, which you can see some of the names of them on the bottom so we're not asking people to do something they don't know about, and then the physician or the healthcare provider gets the opportunity at that point to check it and say, yes, I want to be part of this and I want to contribute it for the secondary use. So the concept is it looks within the data that are already available at the site through the systems and gets everything it can and then only asks the question for the information that's not already there. It does work.

This is an example of a gout registry from the American College of Rheumatology for quality improvement and quality reporting. And here is where you can see how this open standards process works. The forms library comes because it's study based. It populates what you need for the study. Probably the most tested method for this kind of work is what we call RFD, Retrieve Form Data Capture, an open standard for going and getting just what you need. And then once the data are collected with approval, it goes back into the system where it's needed.

Now, this was designed for drug safety surveillance, and it was designed -- this particular program that I'm illustrating here, ASTER, was designed to automate the MedWatch process. And they say that a traditional MedWatch form takes about 30 minutes to fill out. This took less than a

minute. We are now working with the FDA on ASTER-D, which is modifying this for device safety.

Where do we go from here? We needed those uniform device identifiers, so thank you. That's terrific. It's a huge development. We need the accurate device data, and now we have to figure out how to aggregate the data across various sites and various settings. Now that you've settled the device information, hopefully we'll be able to get that recorded in systems.

And then the challenge will be to try to find out how to collect standard and interpretable information from the electronic health information systems and to encourage them that this can -- help promote understanding that this can be done in a way that doesn't violate confidentiality on the part of the patient. I think there are a lot of good examples coming that you'll be seeing and that we've seen this morning. So that's my overview. Thank you.

(Applause.)

DR. RITCHEY: I have a few questions, but I'll try to hold them because Dr. Normand may answer a couple of them. So Dr. Varosy?

DR. VAROSY: Yes.

DR. RITCHEY: He promised five minutes.

DR. VAROSY: You got it. All right.

The key message that I want you to hear is that the promise of

what Ralph was talking about with moving to a model of having multiple uses for the same data is really what we're accomplishing in the VA today. Where the standard registry approach in most cases involves a retrospective and/or reduplicative data collection process that's already layered on top of an existing clinical care process, in our case the clinical data are registry data.

Now, thankfully for us it's relatively easy to get the -- to achieve this harmonization, the NCDR chief science officer, the VA operational chief of cardiology, and the CART program director all in the same room because they are one person. They're John Rumsfeld. I'm not going to talk about that complex harmonization at all and just take it as a given that we're doing that.

And the way that CART works is that it's a clinical health IT tool that improves the efficiency of care by achieving structured discrete data collection and integrates with our existing electronic health record. And it allows people to generate reports in most cases in about a third the time that it would take to do a standard dictation.

The beautiful thing about this with capturing these structured data elements is it allows us to have multiple repurposable data resource that can be used for clinical care for transactional quality management, including things like we do a whole nationwide VA interventional cardiology protected peer review process for reviewing cases when an adverse event occurs, patient safety monitoring, device surveillance, recall management, and then ultimately health services research.

So we've got just by way of showing you some screenshots of the application that results in this standardized text report that we produce at the end, and it then gets pasted to the electronic health record.

What's working well for us? The CART-CL application has been in place for several years now, and for 2011 alone we're talking about 70,000 veterans across the country in all 78 cath labs in the VA had all of their care for Cath and PCI procedures documented. This allows for real-time quality management, integration of data submission to the NCDR CathPCI Registry, and then we have an existing and robust collaboration with FDA already.

Additionally, there's a very well functioning National Cardiac Device Surveillance Program, which is the single largest worldwide cardiac implantable electrophysiology device, or CIED, monitoring program. And to give you a sense of scale here, we're talking about roughly 80,000 ICD remote monitoring transmissions per year, and 28 FTE of staff to take care of the patients across the entire country. That's huge.

So what's missing? Well, to have CART-like applications for the rest of cardiology, including in my area in EP and for peripheral vascular procedures, we would love to have integration of the data resources of CART with the National Cardiac Device Surveillance Program and a better process for device surveillance where the greatest barrier for us, even though we have granular data collection in a number of areas, the greatest barrier to submitting records to the FDA for MedWatch 3500 reports is capturing device

identifiers and, finally, scalability beyond cardiovascular care.

What are our short-term plans? Well, to address these issues in the next three years, we have a few things coming. By 2014 we will have robust CART-like applications for peripheral arterial disease and for electrophysiology procedures. And with CART-EP, which I'm helping to lead the development of, what we're really planning is not just a procedure-based platform, but having an integrated electrophysiology device management platform that will span the spectrum of care from pre-implantation, implantation, in-clinic and remote monitoring follow-up with integration with the National Cardiac Device Surveillance Program.

Also, to facilitate the processes of improving efficiency of care, we're also bringing in real time locator services technologies for cath and EP supply chain management across the VA. This is already ongoing. We implemented this in -- 10 and 11 in the Midwest in the United States already, and this is going to be coming to a VA near you by 2015.

Just to make sense of this, what we're seeing is using real-time locator services, using passive RFID tagging, we'll be able to track device identifiers and what devices are used to facilitate the processes of a number of currently reduplicative data collection steps and dramatically improve the efficiency of care.

What about what's coming in the next three years? Expansion beyond cardiology, including to things such as dealing with in-hospital

resuscitation. And then we're also planning what we're calling CART ACCESS, the Accelerated Cardiovascular Comparative Effectiveness Study System, which is a plan to leverage the CART data collection infrastructure for efficient real-world randomized trials. And so, bridging the gap between registry and randomized trial processes on top of an existing clinical data infrastructure is actually something that's very exciting to us. And that's it.

(Applause.)

DR. RITCHEY: Dr. Varosy, you walked us through some of the history of this. Could you tell us when this was first an idea, when the pilot was first set up, and sort of where you are now? And then, going out to 2016, you mentioned, is to have the full cardiology in there?

DR. VAROSY: Right.

DR. RITCHEY: When did you begin?

DR. VAROSY: What I said was that the whole plan for adding the range of all cardiovascular procedures by 2014, and then beyond that we're talking about other potential applications. But, of course, those will require additional resources that we don't currently have.

DR. RITCHEY: Absolutely. And it's a used system today. What's the history part of that? When was it an idea? When did you start the pilot of this?

DR. VAROSY: This started -- and just full disclosure here. I was still in training when the ideas were formed here, but this really came from

an idea developed by Bob Jesse, who's currently our principal deputy undersecretary, John Rumsfeld, and Steve Finn together within the VA, coming up with this plan for doing this to address in some ways some of the gaps in cardiovascular care in the VA compared to other sources such as CMS to address those gaps. And this process really started in about 2003. The first implementations came in 2005, and by 2009 we had it all implemented VA-wide.

DR. RITCHEY: Thank you. Dr. Normand?

DR. NORMAND: My slides are up, and I want to follow the format that everybody else is following, so I'm tasked to talk about gaps and solutions in terms of methodology and in particular about registries, but in general let's talk about using observational data because that's typically what we're going to be talking about now.

And so, there's well-known problems we don't want to rehash, but we've got the lack of randomization of treatments to patients -- those are devices to patients. We have no control over often registry participation. And that may include the actual patients who come in, it's the clinicians who participate, it's the sites of care. In many -- all the national systems they're voluntary, and so it really is something about that voluntary nature that describes something about their willingness to participate.

And importantly, even the availability of devices, if we look at supply chains within a particular hospital, if we're let's say talking about

vascular closure devices or other devices, not all devices are available in every hospital. And so, you can think of these types of limitations as constraining the system in terms of at least when you want to make an inference or learn about or infer about safety and effectiveness, we have to keep these in mind.

We have missing data. And just as a reminder, missing data is a bigger problem in the observational setting than in the randomized trial setting. And by missing data I'm going to talk about the typical things that happen: missing a data element, somebody didn't fill in this and fill in that, but there's also missing by design. And what I mean by that is a particular registry might be collecting quality of life, and another registry may not be collecting it. And so it's not it's missing, it's not there, but it was missing by design. They had never planned to collect it. And it actually has statistical ramifications that are important.

We now have a unique device identifier, but what we're lacking are the attributes and, of course, getting access to that UDI. And then there are two other statistical aspects I'll mention: correlation and multiplicity. People talk about the big *n*. It's like everyone has a big *n* envy. Let me say the following: that big *n* is actually not as big as you think.

And that is because often when you want to make an inference, particularly about subgroups or effectiveness, the sample size gets smaller. And, importantly, we don't have -- statisticians talk about independent observations. We don't actually have that joy to utilize when we're looking at

observational databases since we actually have to account for that.

And then finally, multiplicity, we heard lots of discussion about multiplicity in the prior few days. And when I say multiplicity, I mean multiplicity in a number of ways. And so, you can think of having a number of outcomes, so several outcomes that are measured. So you want to make an inference about seven different outcomes measured on the same patient, or you may want to compare 18 different devices. And, again, so we know how to handle those. It's not like we don't know. Some people say we don't know how to handle it. Well, actually we do know how to handle it. It's just never implemented. And so, that exists, but not used enough.

So what works well today? And I'll claim that there is a large body of work to analyze observational data, and I'm just going to split it up into within registry and between registry. And you can almost think about this as within data source and between data source.

So when you have a particular closed system, whether that's a registry, you can even think of those within the clinical trial, you've got information about a particular population and whether there's been some control over it. And that control may be just the data collection instrument. So if we're looking at -- let's say the NCDR looking at the CathPCI Registry that has specific elements that have specific rules, and you hope to God everybody's following the same definitions. Those are available. But even within that system, because it's observational, there's treatment selection.

And by that is there's no randomization of devices to patients, and moreover, we need to understand the impact of the selection of the device on the outcome. And there's lots of work that has been done, and I'll talk about a particular in the statistical area and then in the epidemiological area.

More recently -- I don't mean the epidemiological area more recently. But more recently, there's been work in the area of causal influence, and let me underline causal. No matter what we say, we're always cautionary. It's associative. We want to make a causal inference, and so this is why we want to be careful.

However, I'll argue that we're learning to date more about capitalizing or combining information between registries. And it could be between registries, it could be between or among international registries, it could be between a literature review and a registry, it could be between an electronic health record and something else. So, again, mixing the mode of data collection and how the information is gathered and who has access -- when I say access, who's been entered into the system and et cetera. That actually -- that work we know a little bit about it, but we need more work on it.

And so, the groundwork, I think the -- let me say the fundamental work about data harmonization -- how do you define stent thrombosis? And how do you define this? That's absolutely critical, and we

can understand a little bit about who the population is that comes in that registry. And we might know something about practice patterns, but we need more work on that.

And then I would say that there is some work on designing retrospective and prospective studies. And when I say that, it's not to ignore all of the good epidemiological literature that has been talking about case control studies and -- we're now talking about capitalizing the multiple data sources in order to design retrospective and prospective studies. And so, we're starting to do work on that.

But where are there opportunities for improvement? And I would say that between registries -- so I just mentioned that in terms of how do we account for the different designs, the fact that what we know about this -- the mode of data collection or that in some studies it was a retrospective look at filling in the data elements and a prospective look in other data sources. And the audience may be bored to tears when I'm talking about this type of minutiae at this hour of the day, but it actually -- of course, I'm going to say it matters. I'm a statistician and that's what I do, but it really does matter in terms of thinking about how do we account for those design considerations?

And there's also variance components. We know with devices there's plenty of factors let me say different from drugs that we have to account for. There is the operator effects. There is the actual components of

the device. We're talking about systems often and not just a single component. And so there's lots of -- variance components that we have to look at.

I would say that there should be more emphasis placed on designing smarter designs for these types of observational studies. And what I mean by that are utilizing or tapping into looking at control outcomes and control groups. And when I say control outcomes, I'm talking about thinking of an outcome that you should include in your registry or in your data source that shouldn't be impacted by -- that shouldn't be -- the outcome shouldn't be impacted by the treatment. And so, if you actually see that, you know you've got a problem. I'm sure people are thinking about this, but think smarter, think ahead, think about collecting items that would send a signal that there's something amok.

And it's the same thing for control groups. We have comparison groups, but sometimes you can think about select another population where you worry that the variability and unmeasured confounder might be larger or smaller than in another group. And you can tap into that particular group in order to learn about some biases that perhaps you couldn't collect.

I'll talk about another thing called sufficient statistics and just to say the following -- and I think I said this yesterday. We often don't need to know the individual values for each person. There is this need I think to

say we want the risk factors on every single person. Well, guess what? You don't need them on everybody. And sometimes it's sufficient just to know the distribution. And I think we need to get people comfortable with that. We need to get the FDA comfortable with that. We need to get the industry sponsors happy with that.

Of course, you want the detailed data for some things, but not for some questions about safety and effectiveness. Otherwise we would have to collect individual data on everything all the time and that's -- what is statistics? It's about sufficient statistics. So if you tell me a mean and variance, that's all I need to know for some things. And so, again, that's a nerdy statement, but it's statement to say the following: remember, we -- not often, but sometimes -- and I'd say more times than you expect, just having the distribution is sufficient in order to make an unbiased statement about the effectiveness and safety of a device.

What is evidence? This is my usual little time to say something about what do we mean by evidence? What is a measure of evidence? No surprise. It's not a significance value. What do we really mean? Is it the probability of something happening? What is evidence? What is sufficient evidence?

And then lastly -- I could go on, but I'm supposed to stick to my five minutes, which I will, but the -- certainly I think there's other areas, especially listening to -- I'm terrible with names. I forget the first part. It's

Ms. Slipp. I forget the first part, and forgive me. But listening to her talk about what patients need -- and I would claim even what I would need, not even as a patient, but we need to be more visual. And there's a nice field of visual analytics that we should be tapping into in order to convey information to quickly see what's out there. And that's a whole field that I really think is really underdeveloped and I feel could be really, really profitable to this area.

This is my last slide. In terms of -- again, I'm supposed to be talking about the methodological gaps and issues. And so I'm going to deal with the details. And so within one to three years -- I'm going to beg everybody to deal with multiplicity in observational study. And, again, we have methods -- when I say we, I'm talking about the statisticians and the epidemiologists. We know how to do that. Sometimes people don't want to embrace them because they know they're going to get bit by it, but we know how to do it.

The other thing is a better understanding of when -- not understanding. I would say understanding, but for the real world, not the statisticians and the epidemiologists, but when to feel comfortable with using the distribution rather than having the individual data.

And then some protocols for when it would be acceptable to use those supplementary data sources to enhance let me say unrich clinical data in order to make an inference. So when can we borrow information, and when would the FDA, when would industry, when would consumers be

comfortable with that?

In three to five years, I do hope to see something -- more work with visual analytics. And by that is, it would be nice to press a button when I go onto wherever I go onto, Google, wherever, and just say I want to know everything about Device A and Device B and to have it visually displayed to me in terms of the amount of -- I really want that facility.

And that would be the same thing with the registries. The registries, just a nice visual analytic that says -- so information there needs to be more -- this is not my area, obviously, but somebody -- the real smart people that work in that area, that's where we need to go.

And then, as usual, I do think proof of concept, there's a lot of methodologists who have worked on ideas that it sometimes takes a long time to diffuse into practice. And I think the more opportunity that we have to demonstrate proof of concept, the more willing I think people will be able to embrace them when they see those types of results.

Thank you very much.

(Applause.)

DR. RITCHEY: Thank you. Dr. Sedrakyan?

DR. SEDRAKYAN: Sure. I'm going to follow the format that Ralph Brindis had because he didn't follow the exact five-slide part, and knowing that Sharon-Lise was going to talk about a lot of methods and there would be a lot covered, I would like to emphasize just a few points.

I don't think I can come up with something so interesting that we didn't cover before in the past couple of days talking about all the comparative issues and the signal related issues and confirmation related issues, hypothesis, causality. There's a lot out there, and I don't think we can get into all that detail in five minutes.

I wanted to show the background. We developed a framework about how potentially a comparative study based on real-world data needs to address. We really thought about the device factors, hospital and interventionist factors, we thought about patient factors, critically important. We also thought about access factors and media factors, so it is a complexity, but it would be good to have a conceptual framework.

Each time we approach to analysis of a particular registry, you have a conceptual approach to it, you understand what factors are likely to influence the outcomes and the choice -- particularly the choice of a particular type of technology.

As an example of why registries again are important for all comparative assessments, this is an extraction of information from all published trials that compare various bearing surfaces for hip replacement. And really if you look at the evidence that has been published, there would be very little out there and very small studies. The only inference that you can make out of this evidence is that there's insufficient data. If anything, there's no difference between various bearings.

Then, we talked about this before. If you really go into large national repositories of the data registries, you see substantial differences between various bearings and implants. You can identify some subgroup effects, such as larger head size, smaller head size, and some subpopulations. So it's really important for us to consider how do we approach registry data assessment in a way that would be the way for us to go forward?

I really wanted to emphasize again there's a way you can fit in the traditional way of thinking say, okay, what is registry-based study? Is it a prospective study? Is it a retrospective study? Are some of the questions that we want to answer been in the mind of people who set up that registry? Did they collect information thinking that they would really address a particular question so it can fit in the prospective cohort design concept? Or some questions they will be thinking about the later time points, so the information might not be as complete so you can think of it as a retrospective way of assessing -- doing registry-based study.

But the concepts that are critical is really that we need to think about -- and particularly in the clinical fields other than cardiology, that we really come up with answerable questions using registries. They can't answer all of the questions we have. So we'd be careful and think about these research questions that would be supporting some other evidence sometimes, such as biomechanical tests or directing direct evidence from other studies, should be biologically plausible, so it's good to keep that in

mind.

And the two critical concepts, again, measuring the exposure, thinking about misclassification, and how device data particularly within registries, where it's harmonized and based on in future hopefully UDI or catalogue numbers that we have today for some of the products. So if you achieve that exposure harmonization, probably that important bias that is inherited with registry-based studies, that you can address that because there wouldn't be as much misclassification.

Now, the outcomes, Rick talked about can we come up with unambiguous endpoints? Can we come up with something that is hard to define differently? Death was one example Ralph talked about. Implant revision is another one. From patient perspective, I mean which component has been revised, it's really irrelevant. If there was a revision, then there was a revision and people have to go through that second surgery.

And then critical issues that we should be able to address, factors that can influence our questioning mind. Are there any interactions and effect modifications? A particular question we have such as comparing for example that metal-on-metal to metal-on-polyethylene from hip replacement influenced by head size, of age or sex. And then is it possible to learn and replicate findings in subpopulations? And that's also critical to be able to address in the registry-based study. You have really large sample sizes that allow us to do that.

But a key issue is again this -- I mean over and over again, a lot of scientists emphasize the main limitation of registry-based comparative study designs is confounding by indication. And whether it's an Achilles heel or not, what can we do about it?

I wanted to show this evidence from one large registry in New York City and New York State, and it's about selection of particular type of hip implant. And you can see that there's a tremendous variation in selection of a particular type of implant or a bearing even among large volume surgeons or lower volume surgeons. It's hard to say that this selection is related to any patient characteristics. Often what we're dealing with, the products have been selected based on individual surgeons' preference.

Sharon-Lise alluded to another potential way this can happen because of a supply chain. It might be available in a particular hospital. I argue that it's an important concept that needs to be exploited. And we included this -- in fact, Nancy is here and Sharon-Lise -- we included this particular tool and advice in a guidance that has been published in *Value in Health* about how to design potentially prospective studies and analytics related to registry-based prospective studies.

Here's another example. A particular technology is used in 100 hospitals almost exclusively on all patients. In another 100 it's used on almost none of the patients so none of the patients have been selecting this particular technology. Who can tell us that there's such an important

confounding by indication here? I mean is it really that there's a selection going on based on patient characteristics? I argue that it's hard to make a statement. And evaluation of this factor of selection of a product can really help us to design very high-quality observational comparative studies based on registries.

Here is one example of exploiting this variation in care. Within Kaiser registry, we did a study. When we look at the selection of hard-on-hard endpoint, which was again this orthopedic example, metal-on-metal or ceramic-on-ceramic implant, versus hard-on-soft, which are metal on polyethylene or ceramic on polyethylene implants, 0 to 100% variation in practice, so a lot of selection might have been related to a particular preference of surgeons. So we're able to adjust for these confounding factors, and we are more confident that in fact there is no residual variation anymore that can substantially affect the findings that hard-on-hard bearings were potentially associated with strong trend towards higher revision occurrence compared to hard-on-soft bearings. So -- an illustration of that.

And, really, the main goal that I have with my presentation and the statement that I would like to make, evidence is never going to be perfect. We need to learn to make these decisions based on not so perfect data. And really only continuous evaluation of products -- there have been many in the market, thousands of them -- allows us to ensure progress and build this evidence-based innovation. I really draw a parallel with the

Hedralian (ph.) cycle of how we move forward.

I think there's a parallel here, again, I believe to make decisions is the only way for us to move forward. I know I'm injecting the hardcore philosophy in here. Apologies if it's beyond what we need to cover today. But, again, going back to why this is important, here is one particular product that is a knee insert used in knee replacement. And if you look at the various components and attributes, you could come up with 20,000 different types, so it's not reasonable even when you come up with a categorization to do so many comparative trials.

We need to rely on only observational data, try to exploit anything we can, and create some tools to be able to address comparisons and come up with the best controls that can help us to move innovation forward. Thank you.

(Applause.)

DR. RITCHEY: I have one question for you before we move on. You talked about the question that there needs to be a realistic answerable objective within a registry. One, does that imply that the question can be answered? And if so, what does that mean as we move forward?

DR. SEDRAKYAN: The question can be answered, and what does it mean?

DR. RITCHEY: What does that mean as far as the data? What does that mean as far as evidence generation and that type of thing? As we

move forward, what are we going to do with these registries once we have them and we've answered a question?

DR. SEDRAKYAN: Again, I mean the main issue here is that when we ask a lot of our colleagues and the clinicians and scientists, they might come up with the concepts, that is, concepts that really need to be translated into a reasonable question. That's what I meant by that. And because registries capture real life, I think they have the capacity to answer those questions, but we need to have an approach that will make sense, be based on some other information out there.

It can be in direct comparisons on the past, some plausibility -- biological plausibility is really important to keep in mind any other tests that can inform us to come up with these questions. So it wouldn't be a -- clinicians know best, of course, which questions to answer, but we need to make sure we can answer them -- put them in answerable format.

DR. RITCHEY: Thank you.

DR. NORMAND: Can I disagree?

DR. SEDRAKYAN: Sure.

DR. NORMAND: Not disagree, but add to it. I think that -- and I'm not going to take too much time -- but clinicians certainly know what questions to answer, but I think there are other questions that may -- you say physicians know best. They know best about certain types of questions, but there may be patients that have other types of questions and regulators have

different types of questions.

So just to emphasize that, I'm not trying to be argumentative, but the fact that sometimes I think -- especially in the postmarket setting, I think there might be a different set of questions. It's not to minimize, of course, physicians know what to ask, but I think there's a different -- there's a bunch of different stakeholders that enter the arena at that point.

DR. SEDRAKYAN: I can't argue with Sharon-Lise. I'll be in trouble. We work together.

DR. RITCHEY: Ms. Reed?

MS. REED: This session is about optimizing performance. Dr. Dreyer mentioned a hypothesis. I will call it a hypothesis, which is combining UDI with the interoperability will improve efficiency.

And it's my job at FDA, does it really does improve efficiency. And in the course of doing that, UDI is seen as a foundation to something larger, which is an attempt to master the data at CDRH. In the master data management strategy that we began, we engaged a contractor to develop a strategy for us, starting in March of this year. It is coming to an end. And so, we have a strategy that we're moving forward. We're at a point that we're going to start a pilot. And I'm going to use most of the time today to talk about that pilot as we move forward.

The goal is to improve mastery of our core business data at CDRH. We currently have, just as everyone else does, silos of information.

Device identification information is different in each of our different databases. And so we are working toward an effort to improve and institutionalize our data quality processes, incorporate data standards into our IT development work, and improve the ability to efficiently share information across our Center.

What's going well? As I said, our strategy development is complete. We are connecting dots inside the Center, identifying internal stakeholders. These meetings have helped me to identify some additional external stakeholders that we can work with. We are ready to establish a data council in the Center to work on data governance issues and work at further improving quality. And the pilot that I was discussing, we're going to take one type of device, an implant device, and we are going to work on improving that device identification, establishment identification, premarket submission, and clinical trial data. We're taking one type of device to make this a manageable process because we're going to attempt to do this over a six-month period.

What is missing? Within the Center, what's missing is a communication and rollout. So a lot of cultural changes, as you can imagine. And probably it's true in every organization, this notion of master data management is just taking hold in organizations where you try and attempt to move from silos of information to mastering it. So it's taking data and saying this is Center-owned data as opposed to this data is owned by the

registration and listing database, this data is owned by the recalls database, this is owned by premarket.

We are working every hard. We currently don't have a notion of data stewardship, so we lack the properly trained resources to do that. We don't have the data processes and tools to actually profile the data within the Center. We're working towards that. And there aren't that many healthcare and government success stories that we can pull from. To be honest, you want it to be provocative. So looking outward and trying to find journal articles or case studies -- I'm actually on Friday going to go talk to someone at the IRS who has implemented master data management because I want to talk to somebody who's successfully done this and learn from them.

Short-term plans. The six-month pilot, we will be establishing the data council. We're going to operationalize what's called data management principles in the Center, ensure that data quality and standards processes are followed as part of the IT project approval process, and look at and ensure that the data are unique, consistent, correct, and available. So that's part of our data management principles.

We are going to define these data steward roles as part of data council work. We have training set up in the fall. We have some folks going to training this week on data stewardship. Those folks, those data stewards, if you haven't heard of that role before, which I've just learned about, actually look at the data level, at the data elements -- so for UDI, for example,

for device identification, it's the brand, the model, the device description, the product code -- and work through and make sure that it's accurate.

My greatest fear is that the data coming into the UDI database is not validated properly, is not high-quality data, and every time I go to a conference like this and I see UDI slides -- UDI mentioned in every slide set and the reliance on this data, this is why this program is really very, very important. And I talk about it daily to everyone in the Center because I want this data to be high quality so it can be propagated with some assurance throughout the electric -- the healthcare electronic environment.

So we are working on these data steward roles, and then what we're intending to do after the six months is evaluate the pilot results to further refine our data management strategy.

Long-term plans are to learn from the pilot to establish a full data quality program, to innovate for the future around data quality, improve -- to take from the pilot, which I haven't described. So what we are going to do is take implant data that's going to be coming into UDI data for the demonstration project, UDI demonstration projects. We are going to have actual real data from manufacturers on implants.

And we are going to look at that data on those products to our internal systems and say how is that device -- how was that device look described about model, brand, these attributes? So I'm talking about when it was approved. When we get adverse event reports about that device, what

did that device description look like? When we had a recall maybe about that device, what did that look like? And we're going to have these data stewards going through and seeing where there are inconsistencies through our databases and working on quality improvement processes to improve the quality of that data.

We also have plans -- and I had a call this morning -- with other parts of FDA so that we share this notion. We want CDRH to be the governance center of excellence, so we are learning about these data steward roles, and we'll share that information with CDER, our Center for Drugs, with our Office of Information Management. And then in the bargain we're working on getting some data profiling tools from CDER and other parts of the Agency.

All of this is going to inform our total electronic submission efforts, not just submission of UDI data, but as I said of recall data, registration and listing, premarket applications, so that we can have a uniform data management across the Center. All of this will lead to enforcement and adoption of data standards. That's it.

(Applause.)

DR. RITCHEY: This data steward person is a new concept for me as well. You mentioned two different things, or maybe you mentioned one thing and I just heard it differently.

One is looking at data that's real data that's coming in in many

different databases and making sure that it makes sense across all of the different databases. The other was for each option of a data element, making sure that that option matches back to a single thing. Are both of those included in this job or just one of those?

MS. REED: A data steward is really literally what that means. They are the stewards of the data. They will advocate that that quality, that data is the highest it can be. Though right now what happens in the Center a lot is data will come in and there will be folks on the back end -- so the people who are looking at adverse event reports have to deal with some data quality issues, and they fix it at their desk. And then -- they fix it at their desk, and that's about the only place that it gets fixed.

So a data steward would take those data quality issues from an analyst person looking at an adverse event report and speak among themselves so there would be a group of data stewards who would be discussing data quality issues across these different databases. And then if they can't resolve data quality issues, that would go up to the data council to be addressed at a Center level. So it truly is getting to focus on specific data elements and making them high quality as Center-owned data.

DR. RITCHEY: As each of you were speaking, I was thinking about this concern that we have these ways to put data into a system, we have ways to do research at the back end, we have all of these questions in both of these places, and yet Dr. Dreyer mentioned that much of this data is

unreliable, especially as we start moving beyond claims, beyond things that are -- have been more researched.

As we look into the uncertainty of this electronic health data, this seems one way to think about how to include and ensure that there is reliable data across the board. But it's worth thinking about best methodologies and best practices. What are other things we should be doing?

DR. DREYER: And can I get in a qualification?

DR. SEDRAKYAN: Yeah.

DR. DREYER: I don't want to say that all EHR are unreliable because I don't believe that. I think that you need to be thoughtful in how you interpret what you see, and that's the issue about reliability. So not assume that your definition is exactly how it's carried through, but understand that it's not collected with uniform definitions. I need to first correct that.

DR. NORMAND: Can I give you a fact? In Massachusetts we had mandatory reporting of cardiac surgery and coronary interventions. And so, I'll give you an example. For coronary artery bypass grafting surgery, shock is a key variable. The STS has a very clear definition of what shock is. It's been vetted, it's been harmonized, the whole -- we adjudicate shock. When I say we, the physician volunteers come in and adjudicate every single case of shock for the entire state, for everybody who underwent CABG

surgery who's 18 years of age or older at a non-federal institution.

Half the time we have to code it back to no shock. And it's not because anybody's purposely upcoding. It's because data managers change -- so it's just one of these realities when you think about key variables. Even in a registry where it's trained, there are tools -- Massachusetts has somebody who meets with the data managers monthly. This is all at the cost of the hospital.

And so, just one of those things I just sort of want to say that let's have some realism in here as well in terms of there are going to be some key variables that you really need to be on top of. And the reason why we're on top of them in Massachusetts, it's not because of comparing different valves or anything like that. It's because the surgeons and the hospitals are being reported on, on the quality of their programs. And they have an interest in ensuring that their hospital programs aren't shut down.

DR. BRINDIS: I have two comments, and these are all excellent comments. One, as the stakes go up for all the different people involved, whether it be the research people, whether it be the clinicians related to public reporting, whether it be -- whatever the issues are, I've been impressed that the quality of the data continues to improve. In terms of our registries, I'm not sure how it is -- it came sooner for the STS.

As the physicians have become more accountable for the data -- before they were not interested in the data. Now with public reporting,

now with issues related to examining their care related to appropriateness, physicians are beginning to show attention interacting with the quality analysts so the quality is higher.

We have actually through our auditing strategy published abstracts related to the quality of their data, and I think related to Sharon-Lise's comments, different elements have different levels of quality. And those definitions that are more fuzzy, that involve interpretation by data analysts or clinicians, particularly as you point out shock, it's a tough issue. And so those that are particularly involved with -- that are involved very importantly in risk adjustment or related to mortality need to have extra attention. These are in addition to the issues that you talk about related to UDI.

DR. SEDRAKYAN: Can I say something? I think this is the important message. Again, Sharon-Lise obviously adds a level of sophistication and complexity to this. But I also believe that we shouldn't be simplistic, but the messages that come from really excellent scientists shouldn't be clouding and confusing to clinicians. We shouldn't come up with this confusion and clouded thinking. It's really ideal -- the process that we're going through, the mental process can backfire in terms of this trust for the data that is being developed, and it's not the case.

This data is often very reliable, and we can answer a lot of questions that are clinically important to move care forward to improve

quality and delivery of the care forward.

DR. DREYER: I would echo that with giving you the phrase "fit for purpose" and keep that in mind. We've heard a lot of examples of a range of things that you can study in registries and some are -- some elements need that what I call source data verification or clarification or validation. Some don't. We heard from Dr. Evans this morning about using registries for decision making. Another Massachusetts example is Get With the Guideline stroke program. It operates in all the hospitals.

The idea is that you get -- it's a quality improvement program to get faster treatment once you're admitted for a stroke. It hasn't had extraordinary data quality verification, but it's proven so successful that now in my state, if you're having a stroke and you get picked up by an ambulance, they have to take you to a stroke center participating in this program because the outcomes are so much better. So there are some things that you could measure simply, fit for a purpose, and get good answers that make a difference to public health.

DR. EDWARD: I would point out, of course, we get a lot of resistance to audits and to public reporting, and that is okay. Because when people complain about these things, when they say, well, no, that data are wrong and I'm going to go back and I'm going to look and I'm going to prove you wrong with whatever information they want to refute it with, that's okay because you've gotten people engaged. You've gotten them involved in the

system, and that is really a key element in and of itself.

DR. RITCHEY: As you've integrated, Dr. Varosy, the registry piece into the EHR piece, have you noticed that there has been an increase in the validity, the reliability of those data or -- have you looked into that?

DR. VAROSY: Well, what's interesting is that the data that we collect are the clinical data, so it's not a translation process of clinical data to the registry data because it's a one-to-one relationship. What you can do -- and this is where -- all of us wear multiple hats as health services researchers, NCDR roles, professional society roles with ACC, HRS, and others as well as our VA and health information technology roles -- one of the things that you can do is actually develop the graphical user interface formats and structure data entry forms to be concordant with whatever harmonized data own the definitions you have to facilitate data collection that fits with whatever data definitions you have.

In addition, we have features such as embedded links where you can easily get to the CART data dictionary to pull up definitions in real time at the point of care where there are real questions to do this. So I'm not saying this is perfect, but there are ways of actually doing things to allow for facilitated employment of data harmonization in very practical ways that don't add to an enormous amount of effort.

I do ICD cases both at the VA and at the University of Colorado Hospital, and I can tell you it takes 30 minutes or more to fill out the data

collection forms for the NCDR or ICD Registry per patient. And it's a combination of me working with our nurses in the EP lab and our data managers, and it's a cumbersome thing. And so for us to have the ability to in under 90 seconds capture everything that we need to do for the pre-procedure H&P, for the pre-procedure data elements embedded into the process of care, is an extraordinary thing.

And I think it's actually doable well beyond the VA, given enough buy-in from the vendors of the electronic health records, from hospitals, from individual physicians, but obviously it's a much more complex thing than it is for us to do this in a single healthcare system with single operational and clinical leadership.

DR. NORMAND: It wasn't my intention to sound negative, and perhaps I did sound negative if 50% have to be recoded. My point there was that even with a structured -- and it's still going to sound negative -- but even with a structure instrument with a lot of attention, again, having people really buy into it is extremely important. And the practicalities of the clinic are people are coming and going. And to make sure that they really understand it -- the stakes are high.

And when the stakes get high you can't say -- shock is shock, but if the stakes are high, that by the way you're going to be identified as an outlying surgeon or your hospital program is killing too many people, you want shock to be shock, the same across the institution.

Again, I'm not -- I wasn't necessarily trying to be really negative, but there's going to be some variables that are going to require extra care, and there's going to be some that it's, you know, a female's a female and a male's a male, and it's not going to matter. It's going to be some diabetes is going to be diabetes, and sometimes no, you really need that information, just to keep that in mind.

MS. REED: I think that's the inevitability of why these data steward roles have developed as we have more focus on the quality of data. It's inevitable that you need someone who's really focused on that as a job.

DR. VAROSY: Well, just to throw in kind of -- to speak to Sharon-Lise's point that we have a nationwide major adverse event reporting system such that at any time, that a death in the cath lab, a stroke on the table, or a patient goes to emergency bypass surgery, major events that are of importance for public reporting, performance measurement, things like that, and also for addressing peer review issues when there are either systems or personal practice issues that need to be addressed, whenever any of those events occur, we have immediate encrypted e-mail notifications of key people in the quality and management leadership architecture for the VA.

And that results in manual review of the charts by key members of the quality and management program. We actually have real-time evaluation of these things. It's kind of along the lines of launching the National Transportation Safety Board anytime a plane crashes. And so, we do

this on a nationwide level and actually get to see on a practical level how the data are performing for major events that are of critical importance.

A similar kind of thing happens when we have device-related events that occur, and we work with Tom Gross's team at FDA as a way of capturing whenever there's a device-related -- an unexpected event related to a device that's employed in a basic cardiology procedure for the same kinds of things.

DR. RITCHEY: Thank you. Dr. Krucoff?

DR. KRUCOFF: Just in thinking about gaps and listening to this conversation clearly in more specifics than today can probably handle, but somewhere along the line, I think we will repeatedly come into the where, when, and how these data, to be meaningful, need to adjudicated or reviewed in some sort of structure. And as I'm listening, one of the things that leaps out to me is that as we think about a national infrastructure, a lot of the solutions that we're listening to, in Massachusetts with volunteers or locally with medical records, we have fixes that help us get in and out of sensitive private health information scenarios that at a larger level could be a nightmare.

It occurs to me that one way to maybe think about this would be in linking data so that it could be reviewed at deeper levels. Who is better suited nationally to handle sensitive information than the FDA behind a firewall?

And rather than come up with probabilistic methods or other pretty good ways that you can do it in a kind of a hands-off way, the one thing we might think about as a structural component would be whether that linking function -- we have a number of predicates I won't go into, but where FDA has actually linked data, deidentified it behind the firewall of FDA, and then can toss it over the firewall as a whole, fully linked but fully deidentified dataset that can be much more easily but much more robustly looked at or adjudicated and reviewed.

One thing maybe to think about on a national level is the degree to which actually FDA could serve as a behind the firewall trustworthy but also able to handle sensitive information in linking claims data with registries or whatever, not probabilistically but really completely. And then tossing it back over a firewall, fully deidentified, where it could be whole and reviewed.

DR. SEDRAKYAN: I want to echo that. I mean, Mitch, that's a very interesting concept. Just to give an example, there's a project that we're doing under Mini-Sentinel trying to link a registry, an orthopedic registry with a claims data. And the lawyers -- it's been six months -- do not agree how identifiable the information -- who's going to ship to who, who's going to do the link. How is all that going to work out?

Now, my question back to you would be, do you think registries and claims owners will trust the FDA to give that data to FDA?

DR. KRUCOFF: So there, Art, I really do think this is the kind of atmosphere that could generate that trust. If all of the stakeholders are involved in understanding how important this -- I'll call it a dimension of stewardship even though that's not exactly, I think, what Terrie may have meant. But I think as long as we use this kind of inclusive process to help everybody understand that in fact FDA may be the only trustworthy and functionally capable place of linking federal datasets, professional registries, possibly even insurer datasets, in ways that help us adjudicate, in ways that help us make them meaningful, that if we use this kind of process, then maybe.

DR. RITCHEY: We did receive one clarifying question from the webcast. And so I wanted to ask Dr. Normand if you can talk to development of distributions for a first of a kind novel device and how that would work?

DR. NORMAND: The question is an interesting one, and I was really talking about in the -- I'm just talking about a comfort level in the postmarket after something's been approved. And so, there's sort of a question about regulatory science, what's needed for a premarket approval of a first in kind.

That's not necessarily a statistical question, but the statistical answer is that if you have the audited data and you have that available, you don't need the raw data in order to come up with your estimates. But that's to come up with the estimates. That's not to validate, make sure all the i's

are dotted and stuff like that, so the answer is can you do it? Yes, you can do it. Will it pass the sniff test from a public health safety point of view if it's first of kind in man or woman? No. But statistically you could do it.

DR. RITCHEY: I heard and I want to echo -- because personally I think this is an important point -- having distributions is sufficient for some things, but only if the raw data, the person level data is validated.

DR. NORMAND: Well, I mean, yes, I'm assuming that absolutely that -- I think that, of course, the data has to be good data, valid data. Because we don't -- that's the whole field of statistics. You don't need every individual observation. You just need a summary.

DR. RITCHEY: Okay. I think we've had a wonderful discussion. Are there any last thoughts that anybody would like to give for best practices moving forward?

DR. MARINAC-DABIC: I do have one question. And that builds on Mitch Krucoff's idea about the role of the FDA as a trusted party. In the context of discussion that we had throughout these three days and going to continue tomorrow, in the spirit of public-private partnership and leadership role of the MDEpiNet in methods and infrastructure and thinking -- and also coupled with the fact that FDA does have 60 statisticians and over 30 epidemiologists, I think that we can have a really powerful pool of brilliant people that can work both at the FDA and in the MDEpiNet partnership.

I'd like you to comment on how do you envision that role of the

partnership in this context? Because I was really intrigued by Paul's comment on how things are handled if something happens and there is a system. We don't have a national system of that kind. And I think a lot of lessons can be learned from each of your particular experience and we can build it.

But I'd like for you to comment on the role of the Medical Device Epidemiology Network as the public-private partnership, as the methodology brain behind what we are trying to achieve in strengthening the postmarket surveillance system.

DR. VAROSY: Well, I can say that one of the reasons that we can do things within the VA system is that we are a single HIPAA healthcare entity, so there is a legal and privacy framework for treating us as a single healthcare system.

It seems to me that if there were to be some sort of avenue to making a centralized data repository, there would be a need to include discrete language in legislation to say that in order to transfer data, you either need to have informed consent or a HIPAA waiver or such and such, or the data are being transferred to FDA specifically to serve as part of a national repository of registries. Because I know for us to move any data from the VA anywhere else is -- it's essentially impossible.

DR. MARINAC-DABIC: And I think that the entire message through this meeting and through the document that we released is that we are not about to centralize the data collection. It was more of a role of the

partnership in the analytical and assessment piece of potential signal if something comes up. This is what I was getting at. Because again this is the change in the paradigm of us being collectively responsible for what the next steps are going to be.

Because again, to stress again, we are building our national system. It's not FDA's system, an HRQ system, or NIH system, but it's our postmarket surveillance system.

DR. VAROSY: And I'm hearing what you're saying, Danica, but I guess I'm responding in some levels to what Mitch brought up, that if we were to try to provide some sort of centralized repository where the data could be then combined in some way to make larger analyses than any one individual dataset can accomplish, I think that would require more than we currently have under our current legal framework.

DR. MARINAC-DABIC: And, again, it may be time to actually challenge some of the thinking behind why we cannot do things differently. I think the -- ultimately when we go back to what Bill Summerskill had mentioned about having a narrative about what you are trying to achieve and what is the alternative, we may actually say at this moment we do not have everything we need in a legal kind of landscape that has to be there.

But I think what is the alternative? Delays in our knowledge about when the signal occurs and delays in FDA's action. We just heard earlier about certain decisions made in the Australian registry relatively

quickly after the data had been collected and the delays here. Again, we also collected and need to tell the story why this is necessary, and I know I'm preaching to the choir, but I don't think we should leave anything really unturned and unchallenged if we are really truly talking about changing the way how surveillance has been looked at.

DR. NORMAND: Again, just to emphasize, you don't necessarily need the individual data to combine for some questions. If this is a postmarket study where -- you don't need to have the individual dataset. This is the whole idea about distributed networks, right? You don't need the individual level data sent. You can send summary data.

Now, that summary may mean data may be different for different types of outcomes because one's a binary event and one's a survival time. But, nonetheless, you don't need to send the individual data. It just needs to be in the right -- adjusted or at the level where it's sufficient enough to combine. That's a topic in and of itself, but just to remind everybody it's not necessary all the time to have the individual --

DR. VAROSY: But here's the specific example. Think about the ICD Registry. We're talking a little over 800,000 defibrillators in this country documented since April of 2006 when the registry began. When you talk about the cross-walked, the probabilistically matched Medicare claims data, now you're talking about cutting that by the number of patients who actually are CMS-funded devices and then further cutting that by the number of

patients in whom the probabilistic match crosswalk can be made because those processes have to be done.

And, currently, you make a one-to-one match with those data because of the issues around data transfer that we're dealing with. So now we're talking about somewhere around -- I think it's a quarter to a third of the potential patients that we can actually use the probabilistically matched Medicare claims data to answer longitudinal analyses. And if we could actually find a way to adjust what Mitch was saying to have a real one-to-one high fidelity match of patients from a registry framework to the CMS claims data, now all of a sudden you could have much more powerfully done and potentially less biased data to address those questions.

And those are the things that I'm hoping we can address by finding a better way to legally combine datasets.

DR. NORMAND: I'm talking about -- I don't want to make it between you and I, so I'll just be quiet and --

DR. DREYER: But I just want to add to that though that this is -- we're talking -- I think you need to keep in mind the idea of sampling.

DR. NORMAND: Yes, I know.

DR. DREYER: You know, you don't have to study every patient to learn something. The question isn't automatically biased because you don't have everyone. The question is understanding who's got into your data collection program and why. And then you make inferences about what you

know about it. I think it's really important to keep that in mind.

DR. NORMAND: I can't emphasize that enough. And I think we're -- we don't want to go back to -- there's been a whole theory to say you don't need the individual patient-level data. If you're talking about combining data in order to identify links for follow-up, well, that's a different matter. I understand that. But if you talking about looking at the quality of the data or something else, then, again, we'll have to have a probability link or have the identifiers. That's not the issue.

The issue is sort of what are you trying to estimate? Depending on what you're trying to estimate, I claim -- it's not just me. I think Miguel Hernan (ph.) here, a lot of the theoretical people here, they'll tell you that no you just need this and this, and you're done. But it just -- we just have to keep remembering that having the individual data -- we don't have to go after that and not on everybody all the time.

DR. SEDRAKYAN: Can I say something? I think this is, again, based on individual questions and individual device. We don't want to have generalized statements about every situation. I agree with the ICD example. It certainly is the best path. I mean let's take an example of national orthopedic registries that we heard today.

Having information on every patient is not about the questions. It's about efficiency. If your main outcome is a second surgery, then you want to have every surgeon participating and every patient information

because you automatically collect information on the revision. It's by virtue of including and having every person participate --

DR. NORMAND: It's a different aspect.

DR. SEDRAKYAN: It's a different aspect. It's an efficiency issue. It can be the same, for example, if a question or if STS and ACC are collaborating to merge and combine their registries and if the outcome after coronary surgery is to see if people have been admitted for a second PCI here is a question that can be --

DR. NORMAND: Danica is going like this to me, but I'll say -- there's a question here, two people. But I would say we have to talk about the difference between completeness of data and the actual sampling frame. Those are two different issues.

MR. LIPSCHULTZ: Yes, Alan Lipschultz, Healthcare Technology Consulting. I just wanted to ask whether or not the patient safety organization may provide some legal framework for taking individual patient data and shielding it, combining it and doing it but still protecting it so that we don't have to create new legislation.

DR. RITCHEY: Thank you.

DR. BRENNAN: I don't want to take too much of your time, but two things that have been said -- one is the probabilistic matching -- the reports have been anywhere between 70 and 85% linkage rates on the 30%. And the patients who are linked, when we compare, at least their observed

attributes tend to be very similar to those who aren't, so just to dispel some -- unless I misunderstood what was said, just to dispel some myth here.

But the second thing is this concept that we don't need data on every patient. I think that's absolutely true, especially when you're talking about sensitivity analyses. If you're looking at, for example -- stenting versus CABG, you want to know what drove somebody to the stent versus CABG. If you have a sample that's representative of your overall, you can infer back to your whole. But I don't know that that applies to the distributed data network concept.

And my concerns with that concept is that the centers that we're sampling are not a randomized sample. They're a convenience sample. And we know from lots of years of history that when you sample a convenience sample, you are opening yourself up to potential bias. And so, the question is how large does that sample have to be before you can get to a stable estimate, before you can get to not only stable variance but stable point estimates? And I don't know that that work's been done. Maybe it has. I'd be interested to see it.

DR. NORMAND: In my mind, at least hearing your question, I would say you've mentioned two -- you mentioned at least three different things. And I would say that stability is not the same thing as bias, and it's not the same thing as sampling frame. And so --

DR. BRENNAN: Absolutely.

DR. NORMAND: Those are all three different issues, all very important points. But the fact is we don't have a national registry on anybody -- on any device because there's not 100% -- unless I'm wrong -- so we will always face that. I'm really talking about who your target population is and who your sampling population is. And I can see Danica is sort of giving me the look, so I'll be quiet so -- it's a great question.

DR. BRENNAN: I'm just worried -- start with something like the STS database is over 95% of patients so that's as close as you get to it.

DR. NORMAND: Of what?

DR. BRENNAN: Of cardiac surgery, so --

DR. NORMAND: Well, we could talk this offline in terms of --

DR. BRENNAN: You start with what's pretty close to a sample, but the question is -- as you say, they're very distinct points, but until you start to move -- until you get answers to those, where is the inflection point where your variance is actually stable, or your second question, where is your inflection point where your point estimates aren't all over the place based on which convenience sample you're getting -- I just would say we need to be very careful when we're talking about moving to a distributed dataset versus what is close to a national sampling system.

DR. NORMAND: Absolutely right. It depends on how you're sampling. Absolutely right.

DR. VAROSY: And I agree with you that of the CMS patients,

the probabilistic matching is about 70%, but when you take the overall registry components for the ICD Registry anyway, there are other payers other than CMS and, of course, there won't be eligible patients to match there.

DR. NORMAND: And you only have the fee for service. And it's not -- I'm not being negative, but we just need to be very precise about the population that you do have. It's an important population, but it's the fee-for-service population and not all of Medicare.

DR. DREYER: We simply -- I can't not get a word in, but we -- the rest of us who operate outside these magnificent systems and these agencies that can say we have spoken, the rest of us who do research, you're always getting volunteers. I mean you get volunteers in clinical trials. What we do in observational studies and registries is we characterize who's participating. And then within those participants, we go for systematic data collection, sequential patients, so you get everybody within your capture system and you characterize who they are.

DR. NORMAND: Ted, say something we want to hear.

DR. SEDRAKYAN: A statistical question, right.

DR. LYSTIG: Well, I just want to go back actually to Mitchell's earlier point about throwing the data over the wall because there's two concepts -- well, multiple concepts, but two of the interesting concepts that I find as a statistician talking about -- one of which is a distributed data

network, which is this concept of saying you have essentially complete data from different sources and how do you combine those in an efficient manner?

The second question is more along Mitch's point, which is saying I have information from multiple sources on the same person, and I want to link that data together, which is a different issue.

DR. NORMAND: Exactly. Exactly.

DR. LYSTIG: But the problem with throwing it over the wall and getting it back is the ability of the person who got it back to then figure out who it was. Now, obviously we really don't need to -- we don't care who it was. We just care that they're distinct. Like you just need to keep track of individuals in terms of separating one from the other. You don't care if it's where that person lived or how old they were or the actual personal identity.

But the problem with having a system where you do combine data on the same person from different sources and then bringing it back is it takes very few covariates before it's relatively easy to figure out the matching that was done. And the way in which the data was collected in different systems, it may have been done with different types of informed consent where the persons didn't agree that that aspect of their data would be shared.

And that I think goes back to Danica's earlier point in saying if it's a public health issue that we should have access to that data, then it's

worthwhile in pursuing legislation that would allow us to get that sort of linkage.

DR. RITCHEY: We're done, sadly. Sorry. I thought that Dr. Krucoff was coming up to say something else. I didn't realize. He's taking over. Thank you all so very much.

(Applause.)

DR. KRUCOFF: So the bad news and the bad news. The bad news is that we're late, so we're going to turn our break into an ad hoc break, so those who want to break better run for it, but we're going to ask all of the speakers to go ahead and come up. And we're going to try and move along also because for those who are on the Internet and who are web-connected, we're going to lose our web connection I think at 5:00.

The second piece of news that I will share is that Dr. Mack has taken off to catch his flight because we are later than planned.

I'm going to ask those who are running to take a break to try and go ahead and head outside. And for those who are going to stick with us to stick with us, but to please take your seats so that we can go ahead and start into another area that I think has been alluded to --

All right. We're going to dive into an area that has been alluded to a number of times. And I think over the past few days as well as today, we've seen the range of different devices and different approaches to registry information that occupy us. But I think as much as we've been talking

about a national structure, we have at multiple times alluded to what about an international structure?

And it is I think very important to step way back and recognize that while in the drug world genetic pools and metabolic vicissitudes can have huge ramifications, that by and large in the device world, with many of the materials that we've talked about, metal, plastics, et cetera, that we're much more alike than we are different around the world. Global collaboration and global integration in a sense has an even high potential potentially than a national, but at the same time, as with everything we've been talking about all week, the devil's in the details.

We're going to start, and I want to thank all of our speakers for agreeing to try and also stay brief and focused so that we can get to the discussion. As we saw from the last session, the discussion can really be more important than the presentations.

We're going to start with Stephen Graves on leveraging international registries for device evidence.

DR. GRAVES: Thanks very much. I'm just quickly going to sort go through what is actually happening with a particular project which is funded by the FDA, and it's called ICOR. People have heard it mentioned a little bit over the last few days, and there will be more on this tomorrow.

ICOR is the International Consortium of Orthopedic Registries. It's an FDA-funded initiative, which began last year in 2011, and it builds on

established relationships between international arthroplasty registries that have existed for many years. And the purpose of it is to assist postmarket surveillance activities of the FDA and also other regulators.

The intention is to enhance postmarket surveillance through maximizing the potential of the current registries, develop new approaches to registry data use, and promote and initiate new strategies and roles for registries. And in addition to that, it brings together and coordinates a worldwide clinical and analytical expertise in postmarket surveillance.

The ICOR focus really is to capacity build by developing and maintaining shared infrastructure, develop standardized data analysis methodologies that can be used in an environment of registry database variability, and develop approaches to enable cross-registry validation and data confirmation.

Individual registries, however, do maintain full control over their data and data uses. And it's very important that they retain their independence and that has been built into this system. There is no imposition on preexisting responsibilities, which again is very important to ensure effective collaboration. And the intention is to value add to current capabilities.

Current ICOR projects are to develop a standardized database of the prosthesis that we used and so that all the registries can share in that developed infrastructure. We're doing two main clinical projects. One is

related to looking at bearing surface for hip replacement, and the second area is looking at mobile versus fixed total knees. We're also doing a smaller project, but an important project, looking at the outcomes of joint replacement in the pediatric population.

Future ICOR projects are that we will enhance real time data delivery for regulators and industry. One of the important areas that we've already started working in actually is to validate prosthesis outlier identification. There's been a number of examples this year where registries have coordinated to do that and to remove prostheses from the market that aren't performing particularly well.

And very importantly, we're working on a project to look at how we can assist in the introduction of new technology through premarket registry nest of trials. And the importance of registry nest of trials is that they are independent, they make use of existing infrastructure as well as the availability of analytical and clinical expertise. Thank you very much.

(Applause.)

DR. KRUCOFF: Thank you, Steve. And so we lost Dr. Mack to his flight times. And I think what Michael was going to discuss with us are the slightly more than half dozen nations around the world who have collaborative cardiovascular society databases.

After we finish, I may ask Art Sedrakyan to just comment on where this ICOR model might go in cardiovascular, but I think we'll try and get

through our presentations first and then, Art, we'll drag you back up.

Just for those who are following the agenda, we're going to flip the order of our next two speakers on the single topic of Harmonization by Doing and start with Dr. Sase, Professor Sase from Japan.

DR. SASE: Thanks, Mitch, and thanks, meeting organizer. On behalf of the HBD U.S.-Japan Harmonization By Doing activities, I'd like to thank organizer for this opportunity.

My slide is presented for the -- the printed one is for this February's CRT meeting, but it seems we have limited time, so I'm going to skip many of the presentation. I'm sorry about that.

So when CDRH Bram Zuckerman came to Japan, he has encouraged Japanese investigators, regulators, all sorts of industry people that the Japanese heart/lung transplantation, although it has a short history and small in number, but has an excellent follow-up range. So we have learned that quality, not just quantity, can contribute to the international medical knowledge.

In Japan we have some medical EverHeart and Terumo's DuraHeart. And so, those innovative artificial hearts or ventricular assist devices, the question is how do you measure innovation? And in addition to the device evaluation, we need to evaluate not just bridge to transplantation patient, but also the extension or expansion of the indication, like destination therapy, that also would be a challenging question to be answered.

This morning we have learned a lot from the NHLBI and Dr. Marissa Miller about the INTERMACS, and then we have David Naftel from the University of Alabama in the audience, so I'm going to touch just briefly about the INTERMACS and then go on to the Harmonization By Doing activity.

As Marissa said, that the Institution of Medicine, National Academy of Science, back in 1991 they have encouraged NIH to establish a registry for the artificial heart and coming waves of innovation. That's where they have started. And then NIH funded and FDA endorsed the safety and efficacy endpoint. And more importantly, as we have learned this afternoon, that CMS has endorsed the coverage by data generation, in other words, payment by data. That was most important crucial element for the INTERMACS. Every patient has been involved through the INTERMACS.

And I'm going to skip the organization of the INTERMACS on datasets, but they have got the grant, University of Alabama, Birmingham got the grant from NIH back in 2005. And then one year later they started recruiting patients. And since then they have been now recruiting thousand patients per year and the number of the implantation, the number of the transplantation, and it was very impressive.

We have actually learned from the INTERMACS annual report that the transition from pulsatile pump to rotational pump was very smoothly done. And a variation of risk/benefit or cost/benefit for the bridge to recovery is also available from the INTERMACS database, so that was very

impressive.

Now, here comes the Harmonization By Doing activities, the U.S.-Japan collaboration. The global harmonization task force, or International Medical Device Regulators Forum, we are living in the globalized world now. And although -- like the pharmaceutical guideline for the Pharmacovigilance Planning, ICH E2E, although we have the medical device guideline, like GHTF, SG Study Group 5 and 4 document, the postmarketing clinical follow-up study has mostly been discussing the meeting room, but the very important thing is the doing. Actually, the proof of concept project to share that was the most important part we have learned from the harmonization activity.

HBD consists of one steering committee and four working groups. The steering committee, led by FDA and PMDA, both two agency, includes the U.S.-Japan regulatory body and academia and the industry representative like AdvaMed and JFMDA.

That transparency and accountability made the Harmonizing By Doing, a very unique and very important scheme for not just premarket clinical trials, but also the postmarketing registry like the INTERMACS and J-MACS cooperation.

And, in addition, Japan may not be able to contribute premarket study very well, but Japan has a pharmaceutical affairs -- which has not just the spontaneous report advance -- system on the good vigilance

practice, but also Japan has reevaluation system on good postmarketing study practice, which means, for example, that we have a wonderful example of the three-year -- first three-year follow-up of the first -- the coronary stent implantation. But the postmarketing surveillance is one of the area which the Japanese investigator has been very familiar with. And, also, that we'd love to publish our data to *Lancet*, if possible.

The Working Group 2 led by FDA's Eric Chen and National Cardiovascular Center's Dr. Nakatani and myself has been assigned to actually make this important postmarketing registry of the artificial heart.

Early discussion has been focused on finding existing groups of professionals within Japan so that we can quickly establish the declaration between United States and Japan. There have been the Japanese College of Circulation or Japanese Society of Thoracic Surgeon, as well as the Ministry of Economic Trade and Industry, Ministry of Health, Labor and Welfare. They have all been working on the mechanical heart assist device.

They came to FDA back in 2006 and then discussed with University of Alabama or NIH to draw a framework for the Japanese version, whether there should be a single database or there should be a two database made to be parallel, so those early discussion has been very helpful. So existing organization was the key.

And let me reintroduce you how J-MACS looks like these days. The funding -- since we don't have NIH, so funding was a very important

issue, but the PMDA actually provided the initial funding for five years. Since their mid-term plan five years, has actually met the vision of the INTERMACS, the postmarketing registry project.

After we found the funding source, we made the governance organization chart including the steering committee -- all the stakeholders has been included in the steering committee, and under the supervision of the steering committee, we made the operating committee, which includes not just the investigators or the site representatives, but also the statistician and the data manager and so on and so on.

The number of the sites are growing and number of the patients. Although we don't have the thousand patient per year, but we are recruiting almost a hundred patients per year, so that's -- actually, we have started recruiting to the J-MACS.

In summary, we have learned that the innovative devices or innovative technologies, the registry is important to continuously evaluate those innovation. And the U.S.-Japan Harmonization By Doing activity helped to establish J-MACS poolable with INTERMACS. And the experience we have learned from this Harmonization By Doing activity not only applicable to the other country, but also to the other technology as well.

One example is the -- J-MACS -- I'm sorry. J-MACS and -- I'm sorry. I don't have to do that. Okay. J-MACS and INTERMACS collaboration is now growing into, evolving into the international MACS, and that means the

two countries' collaboration can actually be generalizing to the -- activity. And I would like to pass the baton to Dr. Jim Laschinger about -- so our experience on the ventricular assist device may be applicable to the TAV registry or NCDR ACC registry as a whole. On that kind of application, generalizability is another possibility that we have learned.

Thank you very much.

(Applause.)

DR. LASCHINGER: I'm John Laschinger. I'm from the FDA, and I'm a medical officer and a cardiac surgeon by trade, I guess. I was asked to give the overall view of what we learned from the Harmonization by Doing project and where we see this taking us in the future based on the lessons we learned and the potential that we see from this process. I hope we'll get that across in the next five minutes.

Basically, INTERMACS and J-MACS, the lessons we learned were that registry type databases could provide valuable information to regulators, both for postmarket surveillance and for device approval. We also learned that in the Working Group 1 project, that we could perform international studies together and that those could be conducted so that we could get simultaneous device in both jurisdictional domains.

The other things we learned that were benefits that were not necessarily expected were that there was great transparency and almost real-time availability of data. This also reflected real-world use and results in

patients that didn't meet the 7 to 10 inclusion criteria and 15 to 20 exclusion criteria that you get in all these studies, so that we really had real-world results in patients. And that was very useful because it provide the generalizability of the results that we saw in more directed randomized trials.

Also, the data could be used to drive clinical practice changes. Within a six-month period, you saw a total switchover of devices from pulsatile type devices to continuous circulation devices very quickly based on data. And that is not likely possible if we had used the standard randomized clinical trial waiting three to five years for it to be completed and then analyzing the data and disseminating it after that. So this was a real-time process that resulted in real-time changes in clinical practice.

Other critical lessons were the key to this was that we had a standardized cardiovascular dataset using uniform definitions across both jurisdictional domains, and so that everybody was speaking the same language despite our baseline language differences. And so that was very important. And we also learned that the registry data could be used for risk prediction in the defined populations in a way that wasn't clear before the project was started.

We also learned that if we were going to use this data beyond broad epidemiological information in practice improvement, that we needed to do a couple extra things that might be called the weaknesses of these registries, and that was the assurance of complete and accurate data

collection and some sort of monitoring or auditing process in place. And that remains as of now probably the weakest point of these registries, is that there is not complete monitoring and auditing that you would expect in a standard device trial. However, the information we got was still useable and predictive of outcomes and was extremely valuable.

We also realized the value of cooperation and buy-in from all the important stakeholders, including the investigators, the industry, regulators, and everyone else who was involved in the process.

Learning all these lessons, we are now from a 50,000-foot view looking at ways to expand this to additional diseases and devices and also involve other jurisdictional domains outside of the U.S. and Japan so that we can have true international device trials and international registries. And we are using the same letters, but we're calling this project Harmonization By Data.

And fortunately for us, the heavy lifting is already being done. The societies and AHRQ are leading the way as far as harmonizing data. For cardiovascular disease especially, there are now some very good and robust definitions that's for almost everything that we encounter. And the ones that come up, we of course meet with and look to conquer on a regular basis so that this is not becoming an obstacle at all. In fact, it's one of the strengths of these efforts.

In the clinical research study setting, we think that we can use

these datasets and obtain complete, accurate, and confidential information in a study setting. And that's going to be something that we have to prove going forward, but we think it's possible. The major hurdle is what data is going to be collected and how it's defined. Once that's conquered, we can work on the second thing I think more easily.

Major initiatives going forward is whether or not we can just use the off-the-shelf databases from the ACC or STS as a standard baseline dataset rather than having a company come in with a whole new -- CRF forms and having to go through the arguments over what definitions we're going to use, what data we need to collect. Is just collecting all the baseline datasets from these databases enough? And that might appear to be the case.

We can then use a modular approach for additional devices and study specific data that will give us the flexibility and scalability we need to study specific devices over the long term. And also, hopefully, this will give us the ability to cooperate across jurisdictional domains so that we can have simultaneous multi-national studies done once for device approval across several jurisdictions rather than having separate studies done in Europe, separate studies done in Japan, separate studies done in the United States, all with the same goal and resulting in different timelines.

If we're going to continue leveraging registries with medical device data for postmarket surveillance and evidence appraisal throughout the total product life cycle, that's certainly one of our goals. And that's

obviously the title of this session and what we're looking to do.

The TVT Registry and INTERMACS are both good examples of this. In the cardiovascular domain, we'll be able to evaluate real-world use of innovative technology and hopefully drive practice improvement at the same time without giving up any of our abilities to look at the data critically.

We want to hopefully use this process to explore the expanded use of harmonized registries in the device approval process and hopefully in doing so streamline the process and make it more user-friendly along the way.

Part of this may be the eventual need for us to explore the possibility of international site certification for device approval studies, so that if a company has a device and we have the standard dataset and methods to collect that data, that they can go out and pick between sites in each country that have been certified to provide reliable data so that we know that the data we're getting is true and accurate and complete, and they have the capabilities to perform the study in question. And if that's all done in advance, it could certainly streamline efforts long term.

So then our goals for all of this -- and again, these are long-term goals and certainly nothing that's in place right now, but if we can achieve some of these things, we would be able to prove innovative medical devices earlier and on a multinational basis. Possibly we could certainly have better device surveillance once these devices are in the real-world setting and

not only allowing us to detect early problems, but also allow us to detect early successes so that we can really target effective therapy delivery better.

We want a process that drives timely improvement and innovation without giving up the improved decision making that comes from data so that we can achieve both these goals at the same time. Thank you.

(Applause.)

DR. KRUCOFF: Katia, if you'd be kind enough to introduce yourself as they bring your slides up. I realized that in the heat of the transition we didn't do our formal introductions, which we probably should have.

DR. DONATH: Good afternoon. My name is Katia Shimabukuro Donath, and I'm a regulatory and a health surveillance specialist. I work at ANVISA with orthopedic implants. ANVISA is the National Health Surveillance Agency in Brazil. It's a pleasure to be here today to share with you a little bit about our experience with orthopedic implants monitoring.

This is just an overview about what are the topics that I will cover today. Just to remember that orthopedic implants monitoring, we call as well the GHC project because this is the name of the hospital group in the south of Brazil that ANVISA chose for certain projects to be developed there. This is a pilot project that is ongoing. And so we have some results, and we'll talk a little bit about some conclusions we have as well.

Our regulation is based on three areas interacting with itself:

registration, inspection, and technical vigilance. We have a lot of information about the products, and we wanted to know a little bit more about what is going on in the real world.

What is the quality of the products that are on the market? Are these products produced according to the design and details of their technical files the companies sent to us? What are the influences of other actors besides the manufacturers?

As we know, there are many actors involved between the production -- since the production until the final destination of the product that is the patient. So all these actors are important to the final results, and we want to understand better the influences of all these actors. We want to know -- what concluding proof. So at the end of this presentation, I will show this picture as we see in a different way with the information we have with the monitoring.

In order to answer these questions, ANVISA started in 2010 this monitoring project. On the first step we started with hip systems and knee systems. Our monitoring is based in two parts, maybe the big difference, that we have the product analysis. What is it? We collected or we acquired implanted implants that were of a bone market and sent them to the lab to be tested. So we chose some important parameters on this kind of product and to get a picture of the quality of this product.

And the second, about the registry that we want to know more

about the surgeries or to have records of the surgery to get more information about the life of the product after implantation. So we have two steps: one before of the product as how it was manufactured and after the implant is on the patient.

What is the RNA? This is the registry we have in Brazil. The RNA is this database with information about the surgery, some examples of the information that we had on this registry. But the history about this is that association, Brazilian Association of Orthopedic Implants, started with this registry. But in 2009 they came to ANVISA and they wanted to expand the implementation of the RNA.

And so we worked together so it's both ANVISA and GHC doing a review of the information of these formularies that we had. And we are adjusting some points. For us it was really important to have information to connect to the technical files we have about in the premarket that we have information. We integrated this information, important information on the existing formulary that they had in the hospital. So they had their own electronic hospital or electronic form in the hospital.

In September 2010, 100% of the surgeries at GHC were registered. One important point of this construction process was that all the hospital group, the surgeons, the nurses, everybody of the hospital, and with the help of -- they were integrated and they were committed to this project.

The other part of the monitoring is the product analysis. We

collected this implants on the market. So in total was 67 hip components from Brazilian manufacturers and 66 from foreign manufacturers, and 37 knees, national ones, and 43 imported. So in total we will analyze 213 components corresponding to 54 systems.

All these products were sent to the laboratory. Main tests that we request, it's not just this, but chemical analysis microstructure and dimensional analysis as roughness as well as -- and so on, based on international standards. So until July 2012 we have received 25 laboratory reports, and so the evaluation is not finished yet, and we are still working on this monitoring project.

The current status that up till now with the information off the reports, we had some findings, and some of them we were considering critical, so we had some actions according to this risk. We had some inspections on manufacturers, samples were collected for new analysis, recalls and alerts when we had the high risk points.

Another line that we are working is on the label instructions for use and traceability labels analysis. As we have the products and all this information, we want to crosscheck this information what is in our files at ANVISA and what is happening real world. As well we could understand better how is this information used in the hospitals, about instruction for use, and so on.

We are trying to link all this information of the monitoring with

regulatory information we have. Our RNA database analysis, we are -- a lot of information we have there. Some examples of what we could do is, when it's implemented more long time, is trace -- prosthesis lifecycle, promote good qualification of -- professionals, connect information with product analysis. With the data collected by the monitoring, there are a lot of a possibilities to deal with them and to strengthen their regulatory system.

So some perspectives that we want to expand the orthopedic implants monitoring to other hospitals and as well and continue to collect implants on the market. And we intend as well to do the monitoring for other kinds of implantable products. We could see that with the monitoring, we are getting closer the actions of each area that we have in the regulation of ANVISA. And this information that are generated by the monitoring is impact all these areas.

We believe that all these figures, manufacturers, distributors, physicians, the hospital team are important, and we are trying to relate their data and their work to connect them more and more to promote and protect the health of our client that is the patient. They are the reason of our work, and so these are conclusions about the monitor up to now.

Thank you for your attention.

(Applause.)

DR. KRUCOFF: Thank you, Katia. And I'm sure we'll come back to have some questions.

We'll continue now with Bill Summerskill. Bill, if you'd be kind enough to introduce yourself and proceed when your slides come up.

DR. SUMMERSKILL: Thank you, Jack. Bill Summerskill, one of the editors for *The Lancet.* And thank you to the FDA for the invitation to participate in this shared vision of how registries can be developed.

Now, I'm talking from the point of view of an editor, and for many of you, registries will work as a process of continuous quality improvement. For others, there may be signals in a registry that you would like to have published and available to a wider audience. And that's likely to go through someone like me. Of the 100 manuscripts I receive each week, I need to focus on the three to four that are going to be prioritized for a wide range of international readers.

And in doing that, I need to weigh up the robustness of the study and its importance. And my role in getting that study from manuscript to publication is to minimize the bias within it or to make it as transparent as possible. So much of what I say is going to really be convergent with what has been discussed today. Some other points may be dissonant to that, and I think that's important to realize, that outside this room there will be others who will set the bar at a different level when interpreting data from registries.

And for the record, here is my disclaimer. The name *The Lancet* means two things, and when Thomas Wakley founded *The Lancet* in 1823, he

intended to use it with both meanings in mind. One is a sharp knife to cut our practice. The other is a thin narrow window to let in light. And I think it's that second image of letting in light that is useful when we're talking about registries.

Imagine, if you will, your attic. Now, I'm sure that lots of registries are better organized than attics, but within the attic, there will be treasure, there will hazards, and there will be a number of other prospectively gathered objects without an immediate use to them. And in sifting through that, shining a light through the attic, the narrower and dimmer the beam, the more difficult it is to distinguish between substance and shadow. And with an early signal from the registry, that's what we're trying to do. And no one is going to thank you for publishing shadows, so it's trying to distinguish that early substance.

There are particular challenges that come out of registries, and these will have come up in discussions today. And they come up from peer reviewers and in editorial discussions, things such as the completeness of the registry and also the quality. One of the most important statements that we see -- and this has been pioneered by the Scandinavian registries -- is a statement right at the beginning of audits that have demonstrated the coverage, the completeness, and the accuracy of the data in that registry.

Otherwise we're often left in the situation that we're dealing with real-world data, and sometimes this is as good as it gets. But that makes

one a bit nervous because when is as good as it gets good enough? Earlier today we had this phrase "fitness for purpose" raised. And just because there are data populating a registry doesn't necessarily mean that those data can inform every sort of question that might be asked of that registry.

Accessibility is also important. Who has access under what circumstances? And before the blood pressure rises on my left, I think it's -- there's a problem that people can use data from registries in a manner that can result in lower levels of evidence. And so you have registries as a set of data, but how you use that is very important. And the method by which a registry is interrogated can affect the value that others will place on the resulting evidence. And, of course, registries can be expensive. The more elaborate, often the more expensive to run.

But I think that there are also opportunities with registries, one we discussed yesterday, the concept of registries without borders to increase generalization and to also encourage participation. Registries often are seen as most highly valued by journals when they occupy a defined niche where they can have a unique role in answering questions.

I think it's important also to recognize that registries have an opportunity to contribute to research in different ways and don't always have to be standalone but can integrate with other types of research to provide richer, deeper answers to questions.

And again mentioned today, protocol-driven hypotheses, or if

you like hypotheses-driven protocols, that is, to have a set plan for analyzing the material that's in the registry. Over half of the registrations now on clinicaltrials.gov relate to observational research. And it makes a big difference to have someone read a manuscript if it is clear that there was an established protocol with a good hypothesis which was informing the interrogation of that registry, rather than a report that begins with "we found." Not to devalue exploratory research, but we can make it quite clear from the beginning that the finding was one that was driven with something very specific in mind.

I think another opportunity is linking in registries with individual patient safety. And this will be a great way to see registries. There has been recently the scandal of recycled body parts and the problems that when an issue is identified, such as a hepatitis C contamination, one cannot then track through the registry to the individual patient to provide prophylaxis and follow-up care.

So what is the role of journals within all of this? Well, first of all, editors need to be alert to the strengths and the weaknesses of registry data. And I think, as we heard from Trish this morning from the *British Medical Journal,* by and large they are. We've seen lots of slides where registries have made important contributions to our understanding published in some of the highest impact journals around.

I think it's important that editors engage with researchers and

regulators to help feed back our concerns so that we can maximize the potential to informed clinical care. And this means endpoints that are going to be important to patients, clinicians, and commissioners.

This was done a few years ago in something you've heard about, the IDEAL undertaking. And I don't know if this -- we've got a laser here. Well, you can see in the right-hand three columns that registries can play a real role in documenting innovation so that it can be evaluated, because otherwise we get into this dreadful situation that it's always too early to evaluate something until it's suddenly too late and everyone is doing something or everyone knows about the problem. So I think journals can contribute to developing a culture that looks at no innovation without evaluation. And registries play an early role in that and an ongoing role.

I think journals also have to exercise due diligence because a manuscript that reports from a registry is different from other manuscripts. And so, in fact, in peer review we always make sure that we get a peer reviewer who has used the same registry because registries are not immune to fraud. And it's important that the manuscript that goes forward for publication can be verified as much as possible with those people familiar with that registry as detailing first of all items that are actually documented in the registry and have faced validity.

I think it's also important and it falls upon the editor to present information within the totality of our understanding, and particularly because

data from registries is part of often an evolving scientific knowledge about a device or a condition.

So what does that look like? Well, if we put it all together -- this is a paper we published early this year. It's on metal-on-metal hips from the National Joint Registry of England and Wales, which at that time with 400,000 records was the largest registry for this.

Now, you'll see at the top right-hand side three symbols. The first is the swift, because if we get information that we feel can change practice, we fast-track it, and that's the swift signal. That means our goal is to publish within four weeks, 28 days from receipt of a manuscript, a fully peer-reviewed, fully revised, fully edited manuscript. You'll see the web symbol. So this was put on the Internet as soon as it was available to speed dissemination. And then you'll see the cursor with a plus sign meaning that there is additional material on the web. Why additional material?

Well, as those of you who use registries know, you don't just do one analysis. There's a whole series of analyses. So we want to provide a platform in which the authors can post a supplemental but peer-reviewed web appendix in which all the other additional studies, looking at confounding, looking at alternative explanations, can be posted so that others can understand the exploratory nature and satisfy for themselves that the association that's being identified here is one that is credible.

The other thing is to put the research into context so we

publish a panel. What else is available on this topic? Where did the authors look with what search terms so that this can be replicated by readers to convince themselves of how this finding fits within our previous understanding, and then under an interpretation section, how we can use this new information to inform future research or future care.

And, finally, we go out and find a big beast in the field like Art who writes a comment -- and you'll see on the right-hand column of this slide when you go to this paper on the website, there is a commentary linked to this paper by Art. That then tries to set some context and say what does this tell us about the device, about regulation, about registries?

Also linked on the same page is the correspondence because science progresses as a dialogue. And I think nowhere is this more obvious than with registries where you are putting out new information for others to consider and to build upon. And, therefore, to present it in its totality like this helps to desensationalize what could be early and sometimes not always substantive signals that come out.

So I think these are just some ways in which editors can be engaged in the process, can help to promote the best quality of reporting, can use their influence to make sure that peer review is careful and thorough as possible for data from registries, and then to present a clearly reported paper in a manner that shows the totality of understanding and how this can take the subject forward. Thank you.

(Applause.)

DR. KRUCOFF: Our final presentation this afternoon, and Danyi, if you will again please introduce yourself while your slides are coming up.

DR. ZHANG: All right. My name is Danyi Zhang. I am here not only representing our institution, but also representing the Chinese Medical Doctor Association, which is kind of similar to AMA and is -- the Doctor Association has 36 chapters by disease area and 38 chapters by regions across the country and it has a membership of about 2 million physicians, registered physicians. But since I'm the last one on the day, the presentation, I'm going to put my bottom line first.

It is: first, we're coming a long way from China; second, we're big, big in terms of population and growing in economics; and third, we're very enthusiastic about the using of real data, real-world data to inform medical choices; fourthly, we're here to collaborate credibly with FDA, collaborate with various different organizations, and those of you in the audience who were very open. So with that you can go to sleep. So it's really just information now.

I'm going to just talk about -- these are the topics, but I'll skip a little bit here. First of all, I think most of you are familiar with China. It's big and it's kind of muddy, but really I wanted to let you know the thing is, of course, everybody know about Great Wall. It's very symbolic, but it's history. The country has lots of history, so, therefore, it's hard to change. Wherever it

is needs to be changed, it's not easy to be changed.

But economic growth -- those of you who'd just come back from China or know about China, it is a completely different world from what you probably remembered since you were little. And it's a huge population. Sheer volume is really -- make a subtle difference of some of the economic and policy change of that country versus this country or European country. And it's heavily cultural, the country, so things that while we've become very modernized, we are day to day on experiencing the culture which make it the modernized, a little more slow changing.

This is the slides given by Minister of Health and the -- a couple months ago when we met in Shanghai. And here they said really it's industrialized country, it is Asian country, and it is a country with rapid lifestyle changing, which means we become more and more westernalized in terms of lifestyle, as well as the consequence of that.

Some of the facts -- these are just some numbers. We have about 1.3 billion people -- in real fact, the number is probably bigger than that. We have about 9,000 -- over 9,000 imported drugs so far. I think the real number is higher growing in just over the last two years. We have about 186,000 domestic drugs and 22,000, over 22,000 imported medical devices that includes implantable and non-implantable. And there are over 6,000 domestic and foreign medical device companies, and it's a huge number.

And the majority of our healthcare expenditure is on chronic

diseases. And, therefore, China has shifted since 2009 from the focus of end time factory diseases to chronic disease management. So the regulator in China called SFDA -- in terms of a device, there is a five years postmarketing surveillance guideline, but I have to say it has not been very well followed or monitored. So there is a policy guideline, but it's not monitored. But it doesn't mean that it won't be tomorrow.

And physicians are the ones that demanding for real evidence in their practice, fundamentally because there are much, much more medical choices facing day-to-day practice nowadays compared to 10 years ago because there are many, many on the pharmaceutical and medical devices developed in this country or western country now are in China. So the treatment environment is quite similar, as I pointed out yesterday. So changing rapidly, where are they changing rapidly?

The issues: We don't have AHRQ in China. We don't have NIH in China. We don't have good epidemiology data systems, so if you go onto the Minister of Health website in China and you see some of the numbers -- leading cause of death, the numbers are dated somewhat. So we don't have a good system to collect epidemiology data, which is something that we are keenly aware. And there are lots and lots of fragmented surveillance data or registries. So what are the alternative based on this?

So MOH is very committed to chronic disease management represented by the Minister of Health's speech at model U.N. -- not model --

United Nations. My daughter is doing the model U.N. -- so the Minister of Health made a very clear statement in the United Nations conference 2009 -- in 2010 that they have shifted the resource to manage chronic diseases. SFDA is committed to novel pilots approval, represented by fast tracking approval for drug and for device.

Physicians are demanding for evidence guiding medical practice. Payer is considering -- began to considering cost effectiveness data in their decision making in terms of pricing and reimbursement and national registry are occurring. So those are the sort of a movement that we have had so far. I'm going to give you quickly two examples today.

And this example here is a national registry named the China Cardiometabolic Registry. It is a registry that organized by Chinese Medical Doctor Association, particularly with the cardiology and endocrinology societies. It is meant to be a national registry. Therefore, when we do the sampling and when we design the protocol, it's all weighted by the population in each key regions. And it is meant to be done in such that in the model that's similar to ACC's, NCDR, or ESC's the European Euro Heart Survey. And it's a registry that in the model, it's corporate industry sponsored, Minister of Health supported, but CMDA, Medical Doctor Association organized.

We're now -- the red line, if you could see, probably not, it means every single heart failure, cardiovascular disease and metabolic

disease are the targets of our registry. And so far we have -- since late 2008, we have conducted four registries. And these are four registries here since 2008, and the number of patients is in red, as you can see. Some of them are cross-sectional, some of them are longitudinal studies, and these happened to be all different types of design in Type 2 diabetes patients. And it's supported by various industry.

And so, moving on from here, the Chinese Medical Doctor Association, using the CCMR as a model, that we're now expending to other chronic disease registry, primarily the cardiovascular diseases and diabetes, stroke, and the orthopedic registry is one of the considerations. Cancer registries and other pulmonary disease registries are kind of high on the radar.

And so, it is a model that MOH has said we support that, and the Medical Doctor Association said we'll lead that, and we required industry's collaboration to make that happen. And the goal is to really create some win/win benefit where we can be better informed in medical practice and the evidence were used for policy establishment. And then fundamentally the patients will be benefit by knowing what's going into their body.

Here's a little bit of a structure of such a national registry. As you can see, we're quite highly utilizing electronic medical records, and as MOH has said to the nation, by 2015 all teaching hospitals are required to

have adequate EHR/EMB. So we're utilizing EHR exclusively, collecting data from multiple hospitals. And the output of such study will go to hospital, to the sponsor, as well as to the physicians in the area.

And apart from the registries, we're now keenly focusing lots of resource government-wise and private sector on disease management, chronic disease management. As you can see here, this is one of the models that we recently designed for a diabetes and cardiovascular disease area, basically trying to utilize the longitudinal registry reports and through generation and implemented data into the day-to-day practice. And a hospital association also demand or recommend for hospital collaboration, meaning teaching hospital versus community hospital. So such a hospital network is part of that initiative as well.

I put this up here. A lot of the FDA leaders and thought leaders are familiar with this, so it's not only the registry that we are beginning to conduct and to organize. We are also attracting leaders from various different countries to come into China to give us experience, to give us some insight. This one of the conference that we -- is doing so just so.

So this is 2012. In March we held the second China Outcomes Research in Evidence Based Medicine summit, so in a short name called CORE. And next year it would be a third conference in 2013. And such conference is really to draw politicians, government, to draw physicians, to draw industry, to draw researcher together to really gain understanding of

the value of a real world evidence and to transforming the evidence into real world practice. And then next year, 2013, our theme would be translating the health technology assessment information into really the day-to-day healthcare decision making.

We are not alone. We need collaborators. So apart from CMDA, VitalStrategic Research Institute, which is our institution, and we have attracted industry leaders, media leaders, to come together to such forum to share the experience and inside the registries and the real world experience. And here's a shot -- and Art and Danica are both in the picture and as well as some other industry leaders.

The last slide here, it is -- require a globe alliance to solve problem of the world. So today we're here to talk about MDEpiNet, and we talked a lot about NCDR. We just heard about Brazil experience, and now we're studying the Asia and the CCMR, NCDR, but I think all of that is really coming together to -- and collect information for our patient who is really borderless.

So I actually suggest or calling for those of you who already couple of steps sort of beyond us to help us to draw on the future research and registry in this sort of a similar format or similar core information, so that as we collect the future information in China, that we have a core information that really can shared amongst all different countries. You know, every country has their own specific information need to be collected, and that's

okay.

But in order to have international level of exchange of information, so I think we should utilize some kind of a commonality, some kind of a common tool or philosophy or concept as we collecting more real-world data because we're here together really for the same goal, and that is to our patient, for our patients, so thank you very much.

(Applause.)

DR. KRUCOFF: So with attention to time, I am going to ask Art to just make a couple of comments about translating the international orthopedics ICOR toward cardiology. And while Art makes his brief comments, I'm going to ask our panelists to think about the question that I'm going to ask, hopefully, to just go around and then probably draw an end to the day.

So my question to our panelists is going to be pursuant to the two questions that we've been posed. When do we need international consortia, and when do we need national registries, is what are the highs and the lows? What are the great benefits of potentially extending this national thinking to international venues? And what are the big gaps or pitfalls that come with that as we get into an international extension of these questions?

So that'll be my question to our panelists, if you'll think about it, and Art, if you would be kind enough to briefly update us.

DR. SEDRAKYAN: The concept comes again from accumulated

experience within ICOR and learning that happened during the past year. And we think that this is really a replicable concept, scalable, and we're making first important steps.

Establishing this concept and idea, we're thinking to start with a workshop that will discuss a lot of these issues, think about our future and how it will look like for a cardiovascular consortium. Think about even small and then grow big, and focus first for example on a transcatheter revolve technology because of emerging registry in our country, which is very well planned and has a lot of collaborators. And there's accumulating evidence overseas. We've seen in the past, two weeks ago, a report said the European Cardiology Association meeting, so I think there's good momentum for us to take advantage and think about worldwide initiative.

Again, data is accumulating worldwide, industries global and regulators are going global with Harmonization By Doing, and I think it's time for scientists also to be together and data holders also to be together.

DR. KRUCOFF: Great. So as we come back to the panel, honestly, 10 years ago I think we could have raised questions as to whether even the ethical standards of human investigations were something that we would want to compile. Ten years to today, I think we can look around worldwide and be very proud that good clinical practice standards now are identifiable and traceable in most countries in the world.

Moving beyond that, what are our issues? We don't speak the

same languages. We have clinical sites with different levels of practice: good ones, bad one. We have many other things, so why pursue this? What's the high point? The goal? On the other hand, where are the pitfalls? Where do we have gaps that we should focus on? John, can we start with you?

DR. LASCHINGER: Well, from the FDA's perspective, obviously we want to make sure that we have devices out there that are safe and effective. Now, at the same time, we also have a public health mission on making sure that our patients or our citizens are not deprived of innovative technologies that are beneficial to their health.

I think registries are an exciting way kind of to balance those two mandates because they allow us to get innovative devices to market faster and yet have a reasonable assurance of safety and effectiveness that is then coupled with postmarket surveillance to make sure that those impressions don't change as the device rolls out into the real world. And when you couple those two things together on an international basis, I think it can take a lot of redundancy out of the system. By speaking the same language of data across all jurisdictions, we can do things simultaneously if we can work together.

And I think the biggest pitfall to making that happen right now is the completeness and the accuracy of the data and the distrust that we might have for overseas sites as far as being complete and accurate and the same distrust they might have for us for their purposes. I think international

site certification may be a big step in solving that problem, but obviously these things are in the future.

DR. KRUCOFF: Kazuhiro?

DR. SASE: Thank you. I think we are all human, so we are getting together here in the room because we need to expand the border of the knowledge of human being as a whole. Although we have to think big, but it's very important to start small. Otherwise we are all -- and just get lost. So think big, start small, and grow fast is the very important thing.

The 10 years experience of the U.S.-Japan collaboration, through those collaboration, we have actually learned -- although it is very important to talk each other in the meeting room and then discuss about the global harmonization or international medical device regulatory forum or those harmonization scheme, we can talk hundreds of times. But the very important thing is although we think big, but we can start small. The doing is the key, and the proof of concept project is the very important place where we can learn.

And that harmonization cannot just going to be the one way, just the catch-up, copy kind of thing, but harmonization can be really a mutual thing to contribute back and contribute to each other so that we can expand knowledge of the human being as a whole. That's about what we are doing now here.

DR. KRUCOFF: Katia?

DR. DONATH: About our perspective, we believe that the -- each country has your own specificities. In Brazil we have, for example, the universal health system. And so, this is something that we consider and the population is very, very -- so we have Indians and all kind of people that -- ancestors, like -- is Japanese descendent or Australian or Germans and Italians. And so, it's a big mixture, Portuguese, African descendants.

We understand that the harmonization is important, but we really need to think as well -- how is the reality of our country, so this is a big point. And, for sure, I think the information that could be exchanged is important that we could learn. We do not need to repeat the same failures. If we are seeing that another country's had the experience, then we could get better using the experience of other countries. There are some points to put in the balance how to deal with these things.

DR. KRUCOFF: Bill, *The Lancet* published Salim Yusuf's overview of worldwide cardiovascular risks, how we're more the same than we are different. Is this a door that opens, or is this a minefield?

DR. SUMMERSKILL: It's both, Mitch. This is a time of globalization. And it's also a time of globalization of disease because noncommunicable diseases are now the prominent burdens of illness wherever you go. And whether you are in North Africa, in the U.S., in South America, in Asia, you have the same challenges: Type 2 diabetes, hypertension, heart disease. Dynamics have changed. The diseases are

becoming common.

We're also seeing globalization in research and that new randomized controlled trial registrations are decreasing in North America, they're decreasing in Europe. They are going to areas where they can be done more efficiently to just as high a standard and much cheaper. So they're going to Eastern Europe, some are going to South America, and they're going to Asia. So we're seeing globalization in research so that the randomized controlled trial that informs practice in the U.S. may well have been done in several other countries. We're already using data from around the world to inform clinical care.

So let's look at what are the highs and the lows of that. The highs, first of all, are efficiencies. Particularly with a country like Japan, instead of having to do an in-country regulation study to replicate research for licensing purposes, you can plan things in advance so you can be much more efficient. By globalizing registries, then there is an opportunity to set very high standards for governance of these registries and high standards for data entry. And some people may be surprised, but 15 years ago when WHO did the MONICA project on heart disease, the best center for quality of results was Beijing.

Now, all these things come with tradeoffs and, yes, there are potential low points. We have issues of sovereignty over resources. We've seen this with influenza samples from Indonesia. And there is a potential of

sovereignty over population data. So that needs to be negotiated with great sensitivity. And I think this is all going to come down to matters of trust, but being pragmatic, they're also matters of self-interest. And at the moment there may be more stents in American coronary arteries than elsewhere in the world, but if that hasn't changed, it's going to change very, very quickly.

And pretty soon there's going to be a situation where if one looks at relative populations, there are more devices going to be used in more people outside the United States than inside the United States. And in order to provide the best early signals for the best possible health care to protect American health, it's going to be imperative to call upon a broader net to look at these early signals, bring them together in cooperative fashion.

DR. KRUCOFF: Stephen?

DR. GRAVES: I guess there's sort of a couple of issues. The need for national registries, I think the point I really want to emphasize again is that national registries are really quality healthcare mechanisms, and it's where there is the need to have a quality healthcare mechanism. So they shouldn't be used across the board. There clearly has to be an identified need that is going to be addressed. And a national registry becomes important when you need to get all the players involved from the point of view of looking at comparative performance, if possible, to get all the doctors involved. That's where you need a national registry.

The importance I think of the international collaboration, I

think that there is a number of things that are really very important about that. We talked about globalization, but the world is actually a much smaller place. And there are many advantages to the registries working together because if they have shared goals, they can actually work together to develop shared infrastructure, which makes their work easier. They can work together to validate their own findings. For instance, if differences are identified in one registry and are identified in a second and a third registry, the strength of that evidence becomes much greater. And so, the ability to do that and do that easily, I think, is very important with registries working together.

The other thing that registries working together does allow is turning out to be quite important is actually an international comparison of the quality of healthcare delivered in particular areas. And by doing that, what you can see is that some countries actually do it better than others, and you can actually learn what is it about that particular country that enables them to get better outcomes.

And, lastly, I think that international registries working together enables them to coordinate their activities and actually undertake new tasks. And we've been given a good example of looking at the outcome of introduction of new technologies. And I think that that's an important area that will grow and expand as registries work together.

DR. KRUCOFF: Danyi?

DR. ZHANG: Just very brief. In addition to what's already been said nicely, I think Bill mentioned a very important feature I wanted to just emphasize again. I don't have exact the citation here at this moment, but the number, I remember, is within next five to seven years, the total number of knee and hip joint implanted in the world, the highest number is in China, so that China become the biggest country that have the highest implants implanted in Chinese population. So with that being sort of fundamental change, it would be unreasonable for us not to understand better those people who are treated with the same device or medication. So that's not even just a need; it's a must.

And, secondly, is that because of the sheer population in other country, and particularly speaking in Asia country, that there are lots of unique environment, which requires some additional research and development. Therefore, if you don't study and study in the same way that we have learned the knowledge in the Western world, we may miss the opportunity of product development, something new for a particular population with other treatment around it. So I think from that perspective that we do need to do international registry.

Why international? Why can't we just do national registry in a little silo? Because we want to be able to interpret the data over there, how is that different from what we already learned here. So if you use the same protocol, same or similar methodology which will enable us to have such

references.

DR. KRUCOFF: Danica?

DR. MARINAC-DABIC: I think one aspect -- we all agree that there are many, many opportunities and many benefits of working together and working together in this registry world. But one thing that I wanted to build on a couple of statements that were made by Art and by Bill and many others during this conference is how important is the trust that we build as we work together. And this is easier said than done, I think.

This collaboration is such a delicate plant that we all need to cultivate every day very carefully because it takes just a little step to the wrong direction and a lot of years of building this can just go to waste. And I'll give you just one example. Earlier this year I was at the International Society of Arthroplasty Society's meeting in Norway as part, of course, of this ICOR international effort. And one of the thought leaders in the field had made a statement how FDA is outsourcing surveillance. Again, with me in the room, I couldn't not to respond. This is not about outsourcing the surveillance. It's really bringing more data to actually this international space that we can all work on.

On another side we face very often the criticism from within when FDA steps and goes out and facilitates the development of these international registries. There are many critics that said that our support for ICOR may have actually been detrimental to the growth of our own

arthroplasty registry in the United States. And this didn't come from our registry, but from others in the field.

I think as much as we focus on what are the objectives and as much as we focus what we can benefit from, I think part of the strategy is going to be how to build the processes to ensure that we are transparent, that we work together. There are different platforms that we can work on in the government setting, in the professional society setting, in the academic settings, and many other layers of how you actually bring about that change.

My hope would be that after you leave tomorrow, that you'll continue to be the ambassadors of this type of philosophy. And your mission as invited speakers is not going to end here, but rather the mission is going to begin when you go back to your respective organizations to talk and help us get where we would like to be.

DR. KRUCOFF: Before we stop, I want to very quickly just ask one last maybe philosophical question, but a question that takes us back to a point that I think we've been pretty diligent about trying to raise throughout this meeting and onward, which is from the patient's view.

Alan Fraser about two years ago with some of us, Andy Farb from FDA and myself, collaborating on an international basis, wrote in conclusion and the reflection on how by and large medical devices appear first in Europe, then with some delay in the U.S. Traditionally, in the past, the very last in the world would be in Japan. Now that's changed.

The basic assumption is that while individuals differ, that as nations, the degree of risk relative to the degree of benefit that any nation would find acceptable to bring a device to the bedside actually does not differ, that the fact that we have devices appearing earlier in some countries and later in other countries is not because one country is more risk averse than another, and in fact, that physicians and patients worldwide are more likely to see the balance of risk and benefit the same or similarly, and that national borders somehow would have more risk averse countries or more risk similar countries.

As an end, from the patient's perspective, is that true? Do you all think that one of the things that we could count on is that as human beings in healthcare worldwide, that if we were all certain about the risk and the benefit of a given device, that we would likely reach that point of equipoise similarly or differently in China, in Japan, in Brazil, in Australia, in the U.K., in the U.S.?

Are we more the same or are we more different in terms of the actual balance of risk and benefit that we would find acceptable to approving a device or allowing it to continue on the market?

Danyi? Are we the same or are we different?

DR. ZHANG: I think from a human being standpoint, we are no different. We're seeking for a quality of life more so than in the past. Perhaps the only difference here is that in the Asian world, our emphasis of

treatment has been mortality, while in the West it has been long mortality plus quality of life. So the second piece, that quality of life piece measurement has not been systemically done, so in that way you can say the risk/benefit is slightly different. But as people are putting the quality of life a higher priority, then the measurement should be very similar.

DR. KRUCOFF: Stephen?

DR. GRAVES: No, I agree that it is actually the same. But one of the interesting things, it's the same when there is difference as well in that certain devices, the benefit and risk varies on the device. There would be certain cardiac conditions where people would think that it's worth taking more of a risk with the device because of the potential problem if you don't have that device, whereas if you've got the situation like hip replacement, there is many, many wonderful hip replacements that are available, so another new hip replacement, the bar has to actually be higher set for that device because the risk/benefit ratio has changed. And I think that the interesting thing is that those differences, though subtle differences, also seem to be the same across the world.

DR. KRUCOFF: Bill?

DR. SUMMERSKILL: I would say that for patients and physicians, quite similar, but we have to remember that health care takes place beyond the physician and the patient, and it's the environment. And I think when you start bringing in environments, you have two important

factors that can modify that effect: one of them being the availability and degree of information to help inform decisions and the other one being the health system, whether it is more universally accessible than not.

DR. KRUCOFF: Katia?

DR. DONATH: Yes, I'm at this point of view of human being, I agree that should be the same for Brazilians or Japanese or Americans. If we agree that benefits are better, we have more benefits than advantage, should be the same. But as we talked before there are some particular points in each country. One example is in the health system we have in each country. So there are a lot of things that could contribute to the risks, and these systems are not the same as well. It's really a point of reality and --

DR. KRUCOFF: Kazuhiro?

DR. SASE: The question from Mitch is I think interesting, but need more deeper perspective, I guess. Learning from ancient Chinese philosopher, the normal people learn from experience, but the wise people learn from history. Isn't that true? If you take a look at the history, your question is too cross-sectional, just a screenshot. Twenty years ago the Japanese, the physicians don't think we have a lot of acute coronary syndrome but we have a little thrombosis. And that was ridiculous 20 years ago, but right now if you take a look at me, I don't have any trouble finding clothes in the United States, so my cholesterol or whatever is maybe much higher than you.

If you think about the history, what was true in Japan 20 years ago, it's not true anymore. The longitudinal view is also important. If you take a look at screenshots, some region is different from the other. That's true. However, if you think about the past, present, future kind of longitudinal point of view, then that question is irrelevant, Mitch. We're all humans.

DR. KRUCOFF: John?

DR. LASCHINGER: I think from my clinician point of view, which was the majority of my career, I think we're all the same when it comes down to it. I think from a regulatory point of view, I think registries are a wonderful way for us to start looking at our parochial interests and seeing if they're appropriate and trying to build bridges so that we can work together and do more effective device regulation and surveillance.

DR. KRUCOFF: I will add my biased opinion that I think actually a very useful metric for us because it's only -- and as a co-author, I guess this is predictable, but it's only because of political or economic or other underlying boundaries and barriers that the degree at which a device can be clearly understood as this benefit for this risk leads to differential global distribution of the same medical device.

I think fundamental, if we start by understanding that we probably would, erasing other cultural or political and economic barriers, that the degree of benefit or the degree of risk of a stent during ST elevation MI

and how quickly that's available at the bedside, the only reason that we would have differences in availability in Europe and delay in the United States or other variations are because of inefficiencies and redundancies and other kinds of barriers, not because any doctor or any patient anywhere in the world would actually want it that way, to me that's a good metric for, as we work together globally, how well we're doing.

And I want to thank all of our faculty and our attendees for hanging in there.

(Applause.)

DR. KRUCOFF: And, again, absolutely congratulations to Danica. I'm brokenhearted to not be here tomorrow, but this has been a fabulous week, and you deserve a round of applause.

(Applause.)

(Whereupon, at 5:19 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

LEVERAGING REGISTRIES WITH MEDICAL DEVICE DATA

FOR POSTMARKET SURVEILLANCE AND EVIDENCE APPRAISAL

THROUGHOUT THE TOTAL PRODUCT LIFE CYCLE

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were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health.

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